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Diseases of the Nervous System

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Section Two - Monograph Supplement

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Reports of Papers

READ AT

The Fifth Annual Meeting

OF

EASTERN PSYCHIATRIC RESEARCH ASSOCIATION, INC.

Held at

WALDORF-ASTORIA HOTEL

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AND

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Foreword

The Annual Meeting of the Eastern Psychiatric Research Association held at the Waldorf-Astoria Hotel in New York City November 3-5, 1960, concluded the fifth year's activities under the leadership of the organization's founding secretary, David J. Impastato, M.D. It was my privilege to have been president during this year which saw the initiation of a "Newsletter" by the secretary and the successful World Tour of 16 of our members who delivered scientific papers in Tokyo, Hong Kong, Bangkok, New Delhi and Jerusalem.

In the course of the year the Association has continued to grow in numbers and to expand its influence and prestige.

The Annual Meeting was well attended. The panel discussion and demonstrations given at Creedmoor State Hospital on November 3, 1960 drew a large audience, both morning and afternoon. The papers on Genetic and Preventive Psychiatry were so excellent that the Wilson Prize Committee could have justified awarding the prize by lot. The award in basic (laboratory) science went to Aaron Bendich, Ph.D., and the award in clinical psychiatry went to Sidney Werner, M.D., in accordance with the Council's decision to divide the award equally between representatives of these two groups of research workers.

The incoming President, Dr. Charles Buckman, Director of Kings Park State Hospital, has appointed full committees whose functioning will assure general participation of our membership and fruitful continuing growth of research in our area. I take this occasion to thank the many members who made this past year so successful.

W. L. Holt, Jr., M.D.

DISEASES *of the* Nervous System

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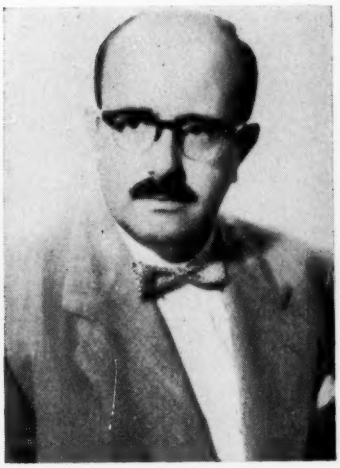

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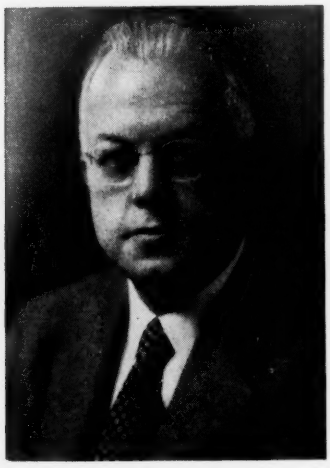

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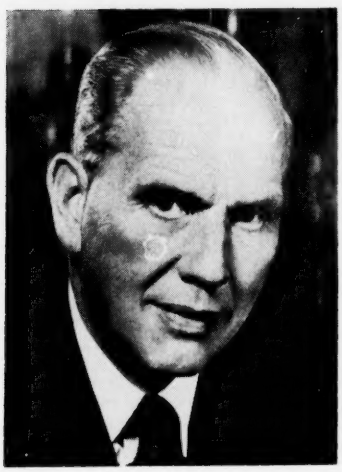

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Studies on the Biological Activity of the Deoxyribonucleic Acids

AARON BENDICH, PH.D.

There has been an intense interest generated in the biological sciences during the past three years following the demonstration that specific molecules of nucleic acids were capable of initiating infections. Molecules of infectious ribonucleic acid (RNA), isolated from such sources as tobacco mosaic[1] and poliomyelitis virus,[2] were found to produce the same diseases as did the parent viruses. There are many examples of this phenomenon[3]. These findings serve to clarify that the biological identity of these viruses is due to their RNA component. Thus, the genetic determinants of these viruses are composed of RNA, of specific structure.

In contradistinction to most of these viruses which contain but a single molecule of RNA, the RNA of the cytoplasm of cells is composed, in part, of the "soluble" or "transfer" RNA which is concerned with the activation of amino acids in preparation for protein syntheses. Another type of RNA, associated with the particulate ribosomes in the cytoplasm, is believed to serve as a template for the assembly of the activated amino acids into proteins in the proper sequence. The current belief is that the latter type of RNA receives its amino acid sequence imparting information from the deoxyribonucleic acids (DNA) in an as yet unknown fashion. Two persuasive mechanisms for the transfer of this information from the DNA to RNA have been suggested: G. Zubay, *Nature*, 182, 388 (1958) and A. Rich, *Proc. Nat'l Acad. Sci.* (U.S.) 46, 1044 (1960).

The isolation of such infectious molecules is important as such isolation makes it feasible to apply an imposing array of chemical techniques to an examination of the basis of their biological activity. As an example, simple treatment of the infectious RNA of tobacco mosaic virus with sodium nitrite produces a change in the molecules which is manifested by the production of mutants in the viral offspring following the infection.[4] Nucleic acid chemistry has progressed to the extent that it should soon be possible to describe the nature of the alteration in chemical genetic terms.

Recently[5] a preparation of deoxyribonucleic acid (DNA) was isolated from the tumor-producing polyoma virus[6] which induces the same disease picture in mouse and hamster cells as does the parent virus. Although this is the first instance of DNA which is infectious, it had been shown in 1944 and several times thereafter that new genetic determinants could be acquired by certain bacteria by mere exposure to the DNA of other bacterial cells.[7] This is referred to as the transformation phenomenon and is perhaps the most direct evidence that the determinants of heredity in cells are composed of DNA. There are many other independent lines of evidence which lead to the same conclusion.[7,8]

To learn more about the chemical basis of the biological activity of DNA and the changes which may result when mammalian cells are invaded by extraneous DNA, a number of experimental procedures were developed and followed.

A—Heterogeneity of DNA[9]

The diversity of the genetic information carried by the mammalian and microbial cell implies a diversity in the nature of the genetic determinants. Although there are approximately several hundred molecules of DNA per bacterial cell, and these are associated with one chromosome, it can be estimated[10] that there are (assuming a molecular weight of 6×10^6) about 800,000 molecules of DNA per normal human diploid cell and these are distributed among 46 chromosomes.[11] It has been possible[10] to affect a partial separation of the DNA into various fractions by means of an ion exchange chromatography.[12] Such fractions of DNA from pneumococcus[13] were found to differ in their transforming activities.[14] Chromatographic fractions of DNA from the calf thymus gland were found to differ in size and shape, in chemical composition, in their response to mutagenic and other agents, and in still other properties.[15-18]

Complex as is a molecule of DNA,[19] the difficulty in developing an experimental approach to an understanding of its biological action is further compounded by the existence of this material in the form of a complex mixture in human cells and the absence of a demonstrable biological

From The Sloan-Kettering Institute for Cancer Research, New York 21, N. Y.

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activity. Examples of the complexity of the mixtures in human tissue are given in Figure 1 which represents the anion exchange chromatographic profiles of the DNA from normal and leukemic leukocytes and normal spleen.[10] It is to be expected that the chromatographic fractions, depicted in Figure 1 as numerous "peaks," also differ in physical and chemical properties. These analyses reveal experimentally significant and reproducible chromatographic differences among the four sources. Differences in chromatographic properties of normal and neoplastic thymus have also been observed in experimental animals.[20]

It is known that DNA-mediated transformation in bacteria can be inhibited by non-transforming DNA from bacterial and mammalian sources.[21,22] Since pneumococcus contains fractions of DNA some of which are and some are not transforming,[13,14] it can be seen that the total genetic expression of these carriers of genetic information will be influenced by the composition of the mixture. Fractions of DNA from mammalian sources have been found to differ considerably in the extent to which they inhibit the transformation phenomenon in pneumococcus.[23] Thus, although genetic transformation of mammalian cells by DNA isolated from other mammalian cells has not yet been observed, it can be anticipated that fractions of the DNA such as those shown in Figure 1 may be endowed with different biologic activities. It is not yet known whether the presence of a fraction of DNA molecules in the leukemic cell which is absent in the normal (or *vice versa*) has anything to do with the leukemia. However, it is known that intrusion of DNA from the tumor-inducing polyoma virus (or from polyoma virus-infected cells) into normal cells renders them capable of causing typical tumors in whole animals.[6] There have been other, perhaps less well-defined, examples of the nucleic acids which are carcinogenic.[24-26] Accordingly, studies on the penetration of cells by nucleic acids were undertaken.

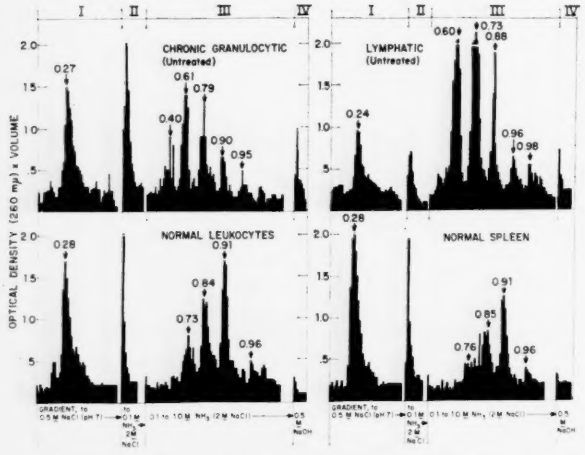

Figure 1. Chromatographic profiles of DNA from normal human tissues and from the leukocytes of patients with chronic granulocytic and lymphatic leukemia. The numbers above the peak in Region I refer to the molarity of NaCl, and those above Region III refer to the molarity of ammonia, used to effect desorption of fractions of DNA from chromatographic columns containing the DNA absorbed on an anion exchanger known as ECTEOLA. These data (taken from reference 10) are plotted in a manner such that the actual areas shown in black are directly related to concentration of DNA.

B—Preparation of DNA for Chemical Cytology

In order to visualize the actual penetration of DNA into human or other cells and to observe localization in specific sites, a labeling technique was required which would be generally applicable to DNA of various sources. The label of choice in cytochemical studies is the radioactive isotope of hydrogen, tritium. It has a long half-life (12.4 years), and its β-particles are of low energy with a maximum path in water of no more than a few microns. Autoradiographic techniques employing strips of photographic emulsion in intimate contact with the histological section can reveal the position of the tritium label within a micron (10,000 Å) of its actual location in the section.[27] For example, this type of autoradiography permits the localization of DNA within individual chromosomes when the simple DNA precursor thymidine, labeled with tritium, is employed.[28]

Labeled DNA can be prepared biosynthetically, i.e., by supplying a tritium-containing precursor to an animal or micro-organism followed by isolation of the DNA after a suitable time. It would be well-nigh impossible to apply this method to the human if highly labeled DNA from leukocytes or nerve cells was desired. An exorbitant and undoubtedly toxic amount of radioactive precursor would have to be administered to a willing subject. Fortunately, tritium can be introduced into isolated organic compounds by simple exposure to tritium gas (the Wilzbach procedure[29]). Accordingly, DNA, isolated from leukocytes and from pneumococci, was labeled by this method. After suitable purification, a preparation of leukocyte DNA was obtained which contained as much as one atom of stably-bound tritium per thousand atoms of hydrogen.[30] This required the exposure of DNA to 0.39 atmosphere of tritium (2.4 curies) for 11 days at room temperature. Comparison of the anion-exchange chromato-

graphic behavior (Figure 2) and other properties of the DNA before and after this extensive treatment (Figure 2) revealed alterations which suggested a decrease in average molecular weight from 5.2 to $1.3 \times 10.^6$ The magnitude of this radiation-induced effect can be considerably decreased by shorter exposures to give labeled DNA of specific radioactivity which is quite adequate for autoradiographic studies. When exposed to tritium for 8 hours, highly radioactive pneumococcal transforming DNA was obtained which retained its biological activity and showed no significant alteration in physical-chemical properties.

Figure 2 illustrates another example of the differences in response of DNA fractions to chemical or physical agents. The fractions differed in their response to the exposure to tritium and in the extent of incorporation of the label. The chromatographic method makes it possible to select a fraction of desired size and radioactivity.

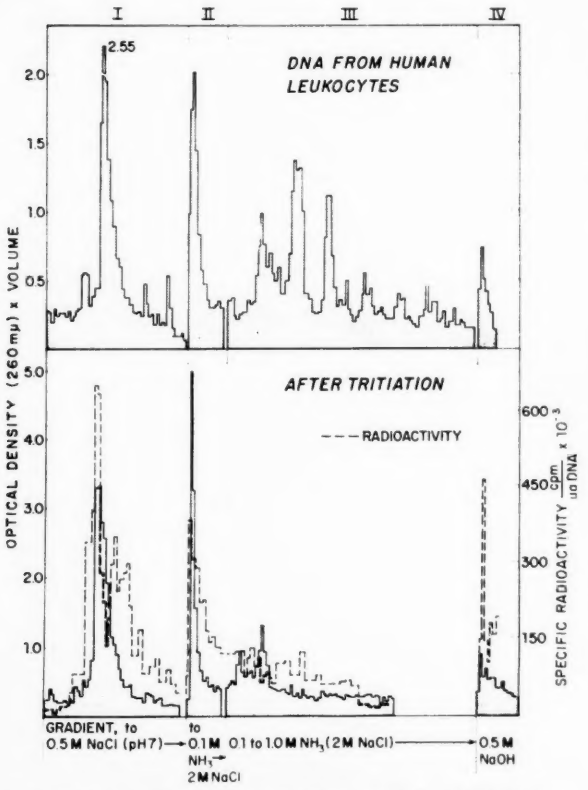

Figure 2. Chromatographic profiles of DNA isolated from the leukocytes removed from an untreated patient with chronic granulocytic leukemia. Upper profile: original DNA; lower profile: after exposure to 0.39 atmospheres of tritium (2.4 curies) gas at room temperature for 11 days. In this plot, taken from data in reference 30, the grey areas represent the concentration of DNA within the chromatographic fractions and the dashed lines the specific radioactivity. If the specific radioactivities of the individual fractions were all the same, a straight horizontal dashed line about half way up the lower profile would have been obtained.

C—Penetration of Human Cells by DNA

For orientation experiments, cultures of human (HeLa) cells growing as monolayers on microscope slides were employed. Sterile solutions of transforming DNA from pneumococcus and DNA from human leukemic leukocytes, tritiated by the procedure described above, were added to the growing cultures in various amounts and times, and under a variety of experimental conditions. After pre-determined contact with the DNA, the cells were washed, and prepared and fixed for autoradiography before and after specific chemical or enzymatic treatment. Films of photographic emulsion were then intimately applied to the cells while still attached to the microscope slides. Depending on the level of radioactivity, the slides were exposed to the photographic film for periods varying from one to four weeks, and then developed. The tritium label is detected by the presence, in the developed photographic film emulsion, of grains of silver (Figure 3). To localize the position of the grains in the overlaying film with respect to the specific cellular structures beneath, the entire slide with adhering cells and film was appropriately stained, and was then ready for microscopic examination.

Examples of autoradiographs obtained are shown in Figures 4 and 5. In these examples, human (HeLa) cells were exposed at 37°C for 24 hours to tiny amounts of tritiated leukocytes DNA or fractions thereof. Silver grains are seen above the cytoplasmic and nuclear regions with decidedly greater localization of the label in the nuclei. There was no labeling when the incubation was carried out at 4°C and this suggests the participation of an active physiologic

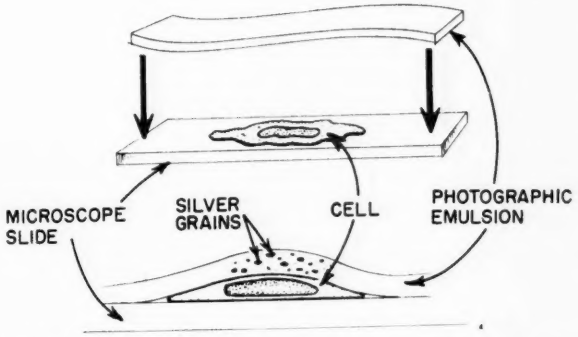

Figure 3. Preparation of specimens for autoradiographic localization of tritium-containing cellular components.

Figure 4. Autoradiograph of human (HeLa) cells grown for 24 hours in presence of tritium-containing deoxyribonucleic acid isolated from human leukemic leukocytes. McNeal's stain; 850X.

Figure 5. Autoradiograph of human (HeLa) cells grown for 24 hours in presence of a chromatographic fraction (from Region I of chromatogram in Figure 2) of deoxyribonucleic acid isolated from human leukemic leukocytes. McNeal's stain; 850X.

process in the penetration rather than a simple diffusion or contamination. The experiments to date indicate that the HeLa cell does not distinguish significantly between the human or pneumococcal DNA as revealed by the extent of incorporation of label. The biological effect of this incorporation into HeLa and other cells is under study.

The presence of tritium in these cells does not of itself necessarily mean that chemically or biologically *intact* molecules of DNA had penetrated the cells and been laid down as such in the nuclei. For example, these macromolecules might have been broken down by specific nucleodepolymerases or other enzymes and the resulting nucleotide or nucleoside fragments, still retaining tritium, could then have been incorporated as is the case with tritiated thymidine cited above. To determine the chemical identity of the tritium-containing moieties within these cells which give rise to silver grains, cells which had been exposed to DNA were treated with the DNA-splitting enzyme deoxyribonuclease and then examined by autoradiography. This treatment removed all the tritium label whereas treatment with ribonuclease or dilute mineral acid resulted in removal of none of the label. It therefore can be concluded that the tritium label was associated with macromolecules with properties expected of DNA. Whether or not these macromolecules were identical with those to which the cells were exposed is now under study. One of the approaches to this question is concerned with the reisolation of biologically active DNA follow penetration. Thus far, it has been learned that an amount equivalent to about 10 per cent of the ordinary cellular DNA complement can be taken up when HeLa cells are exposed for a day to a medium containing twice the DNA content of the cells.

Current studies are underway to determine if such uptake of DNA or fractions thereof by mammalian cells constitutes acquisition of new genetic determinants. Transformation of a normal into a tumor or a leukemic cell via DNA from the appropriate donor source would be an unequivocal demonstration. This type of alteration may be involved in the infection of normal mouse or hamster cells by the DNA prepared from the polyoma virus.[5] Support for this supposition has recently come from the demonstration that interaction of such cells with intact polyoma virus can lead to their transformation into tumor cells.[31]

It is known that entrance of new DNA into cells *via* viral infection, bacterial transformation or fertilization of the egg by spermatozoa, causes

profound alteration in the ordinary metabolic growth and biosynthetic mechanisms. In several instances, it has been possible to identify the new proteins, enzymes, inhibitors and other compounds which the new DNA has instructed the invaded bacterial cell to manufacture,[7,32-34] and which it could not make before because of the absence of that DNA. Thus, a deficiency in a particular enzyme can be rectified by supplying a suitable genetic component. There are heritable diseases in the human which are manifested by a deficiency in certain enzymatic activities.[35] One such inborn error of metabolism is congenital galactosemia in children in whom a specific enzyme involved in galactose metabolism is lacking, and which is traceable to a specific genic defect.[36]

It will be of interest to see whether an invading DNA molecule replaces pre-existing nucleic acid in the nucleus or in a particular chromosome, or whether it adds to these. These questions may have pertinence in neoplastic and mental disease since nucleic acid and chromosomal aberrations are frequently seen.[37-40] A striking example of the latter is encountered in mongolism. This heritable disease has recently been characterized[39,41] by the presence in the cells of mongoloid imbeciles of an easily recognizable chromosome in excess of the normal diploid complement of forty-six. Extranumerary chromosomes are also seen in the somatic cells of patients with Klinefelter's syndrome, while Turner's syndrome is distinguished by loss of a sex chromosome.[38,40] These and more recent observations[42] strengthen the view[43] that mental illness may result from quantitative as well as qualitative abnormalities in the genetic determinants of individuals. The availability of refined techniques for autoradiography and for chromosome examination should make it possible to study these clinical problems at the molecular level.

Author's Note: Most of the unpublished work described herein was carried out in collaboration with Dr. Ellen Borenfreund, Dr. Herbert S. Rosenkranz, Dr. Sam M. Beiser, and Mrs. Grace C. Korngold.

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Tissue Culture Studies of Inherited Retinal Dystrophy

RICHARD L. SIDMAN, M.D.

The study of inherited and developmental diseases of the human nervous system has been hampered by limitations of method. Clinical analysis is essential to define these diseases, but clinical study alone rarely gives a full picture of the main events and causes of a disease process. The opportunity for neuropathological examination of brains with developmental disease is infrequent, particularly at stages when the brain is still forming. Experimental methods may be used for the further analysis of disease mechanisms. In particular, tissue culture offers an opportunity for study of these diseases isolated from some of the complexities of the intact organism. The experimental methods are especially useful when applied to laboratory animals with reproducible developmental diseases, since animal tissues may be sampled at all stages in the unfolding of the disease process.

A number of inherited developmental diseases of the nervous system are known in experimental animals, particularly in mice.[12] Some of these are similar or identical in their consequences to human diseases. We are concerned here with an inherited developmental disease of the retina, the most accessible part of the central nervous system. The mouse disease is an inherited progressive retinal degeneration, and is sometimes referred to as "retinal dystrophy";[26] it closely resembles *retinitis pigmentosa,* the most common inherited cause of human blindness.

The mutant gene "retinal degeneration" has been recognized since 1951, when Brückner discovered that a high proportion of mice in the wild population around Basle were blind. Genetic studies have shown the disease to be present in several strains of mice and to be inherited in all of them as a simple autosomal recessive.[17,26,27] The disease becomes recognizable when the mouse retina is nearing the end of its developmental period.

During the second week after birth the normal retina begins to form rod outer segments. At the end of the second week the eyes open and vision probably begins. The rods elongate progressively during the second to fourth week after birth, and thereafter the retina is mature. In the diseased animals the retina is normal up to the second postnatal week by all histological,[15,26,27] biochemical,[13] and electrophysiological[20] tests made to date. During the second postnatal week, when the rod outer segments ought to be differentiating, development ceases in the diseased retinas, and the entire photoreceptor cell begins rapidly to melt away—outer segment, inner segment, nuclear portion, and synaptic zone. By the third week after birth, most of the photoreceptor cells have disappeared without trace. By the fourth week, the photoreceptor zone contains only a single incomplete row of nuclei and no rod outer segments. The retina never recovers structurally and vision is never regained.

We have been interested in the pathogenesis and etiology of this disease, and have studied the morphological appearance of the retina with a variety of histochemical staining methods at daily intervals throughout the developmental period.[24] This material has given us a description of the daily changes in the retina, but no clue as to the cause of the changes. Stimulated by the reports of Lucas and Trowell[18,19] we began an analysis of the disease by means of tissue culture methods. The present report contains a description of the daily events during the period of rod outer segment formation in normal and dystrophic retinas, and our initial data on the responses of normal and potentially dystrophic retinas to carotenoids *in vitro.*

Strains of Mice and Methods of Study

We used a C3H (pigmented) strain of mice, known to have retinal dystrophy.[9] The mice were obtained from Heston via Grobstein at the National Cancer Institute. Grobstein's and our breeding data pooled brought the mice to the F23 generation when our histological studies were done, and to F27 when the tissue culture studies were done. As controls we used BALB/c (albino) mice (also from Dr. Grobstein) at F22 and F27, and F1 hybrid offspring (pigmented) of matings between C3H males and BALB/c females.

Eyes were fixed for histological study by freeze-substitution[10] and were embedded in polyester wax, sectioned at 5μ, and stained with a combined periodic acid-Schiff and alcian blue stain, as in previous studies.[22] Other sections were stained with sudan black B or with toluidine blue.

Tissue culture studies were carried out by Trowell's organ culture procedure for postnatal mammalian organs.[29] Cultured eyes were fixed in

From Laboratory of Cellular Neuropathology, Harvard Medical School, Boston 15, Mass.

Zenker-formol, embedded by a modified polyester wax procedure,[25] and sectioned and stained as above.

Experimental Studies

Histogenetic Events in Normal Retinas: The patterns of cell proliferation, migration, and differentiation in the mouse retina from the 10th embryonic day to maturity, as studied by autoradiographic methods, have been described elsewhere.[23] Only the 8th to 14th postnatal days concern us here, for the histogenetic events of these days provide the frame of reference for the tissue culture studies on normal and dystrophic eyes.

On the 8th postnatal day the total population of photoreceptor cells (rods and cones) is present in the retinas of normal mice, and formation of outer segments is about to begin. On this day the photoreceptor cell consists, from the inside of the eyeball outward, of a developing synaptic terminal enclosing a giant mitochondrion, a nuclear zone, an inner segment, a cilium projecting from the main part of the inner segment, and a bulbous investment of cytoplasm around the outer end of the cilium. These structural parts of the rod cell have been defined in greater detail with the electron microscope,[16,28] but they can be resolved even with the light microscope in well-prepared specimens.

On the ninth day a new material, clearly stained with the periodic acid-Schiff method or with sudan black B, is seen at the outer end of some developing photoreceptor cells (Figure 1). This material represents the beginning of outer segment formation. During the 10th and 11th days, more and more cells contain some outer segment substance, but as yet the outer segments are only a fraction of a micron long. On subsequent days they lengthen rapidly and form a prominent tissue component by the 14th day. The subsequent rate of growth resembles that described for the rat by Detwiler.[6]

Histogenetic Events in Diseased Retinas: In the diseased mice, all parts of the immature photoreceptor cells are present on days 8 to 11, from the synaptic end to the incipient rod outer segment. The maximum development of rod and cone outer segments which we have seen is illustrated in Figure 2. One has the impression that rod nuclei and outer segments are usually fewer in number in the diseased retinas during these days, but the impression is difficult to validate because both the normal and diseased retinas are more fully differentiated at the posterior pole than toward the periphery, so that comparison of identical regions in both groups is difficult. An increase in ribonucleic acid of the inner segments in diseased retinas, suggested by electron microscopical observations,[16] was not detected in

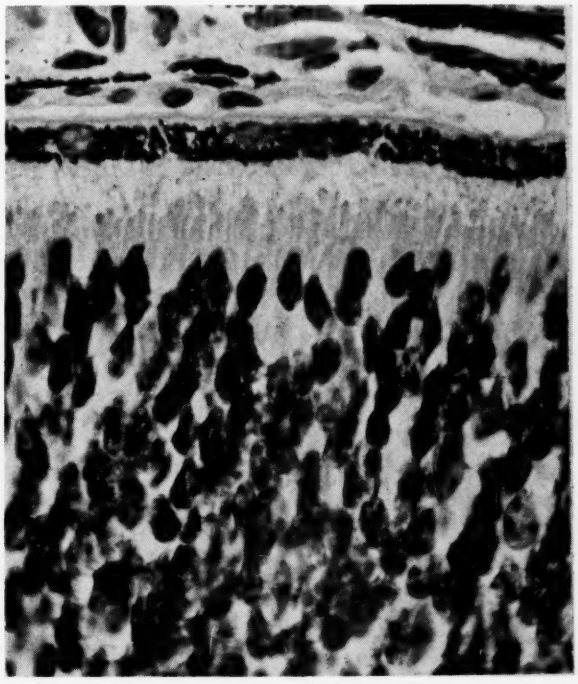

Figure 1. Normal 9-day-old mouse retina. Photoreceptor inner segments project through the outer limiting membrane and terminate in bulbous expansions. Some periodic acid Schiff-positive outer segment material has been formed. 1200X.

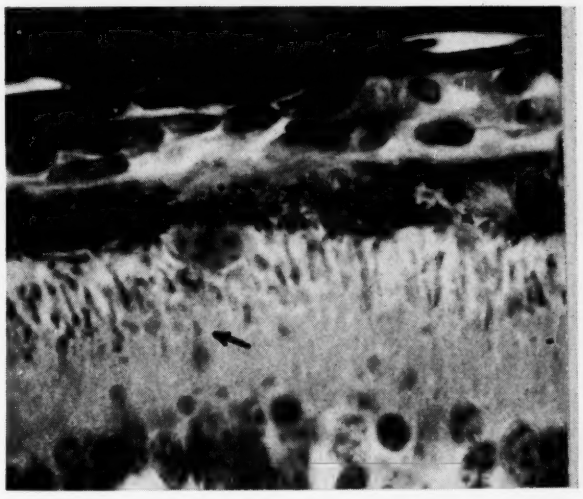

Figure 2. Dystrophic 11-day-old mouse retina. This eye shows the maximum development of rod outer segments which we have encountered. Arrow points to the ellipsoid and outer segment of a well-developed cone cell. Above this cone cell, between the rod outer segments and the pigment epithelium, is the prominent nucleus of an interstitial cell.[22] 1200X.

our stained sections. On days 12 and 13 many photoreceptor nuclei are pycnotic and others disappear. Rodlets and droplets of material stained with the periodic acid-Schiff method may still be seen in the outer segment zone of the diseased retinas, but the outer segments are reduced in number and size. No outer segment material remains on the 14th day, and entire photoreceptor cells are disappearing (Figure 3). The interstitial substance[22] between photoreceptor cells and pigment epithelium appears normal. In old animals no trace of the photoreceptor layer remains; the bipolar and ganglion cell layers are relatively normal, except for scattered clusters of pigment granules within them (Figure 4).

Thus rod outer segment material appears to be laid down on the 8th to 11th days in both normal and diseased retinas, while on the 12th to 14th days the outer segments begin to elongate rapidly in the normal retinas but to disappear from the diseased retinas.

Tissue Culture Studies on Normal Eyes: Eyes of 6 to 11-day-old mice were removed with sterile technique and were placed intact in organ culture.[29] Eyes of 8 and 9-day-old mice were preferred. The eyes were positioned cornea up, usually two eyes per ml. of culture medium. Most eyes were cultured in a mixture of three parts of Trowell's T8 synthetic medium[29] plus one part of human placental serum. The medium was supplemented with all-*trans* vitamin A or 11-*cis* retinene (vitamin A aldehyde).* These carotenoids were dissolved in ethanol and added at a final concentration of 4 or 40 μg. per ml. of culture medium. Control media contained 0.2% ethanol alone. Every third day 10% of the volume of culture medium was replaced with fresh glucose and sodium bicarbonate, as described by Trowell.[29] Cultures were gassed with 95% oxygen and 5% carbon dioxide, and were incubated at 37°C. Cultures were fixed on days 3, 6, and 9 in some series, and on days 2, 5, and 8 in other series.

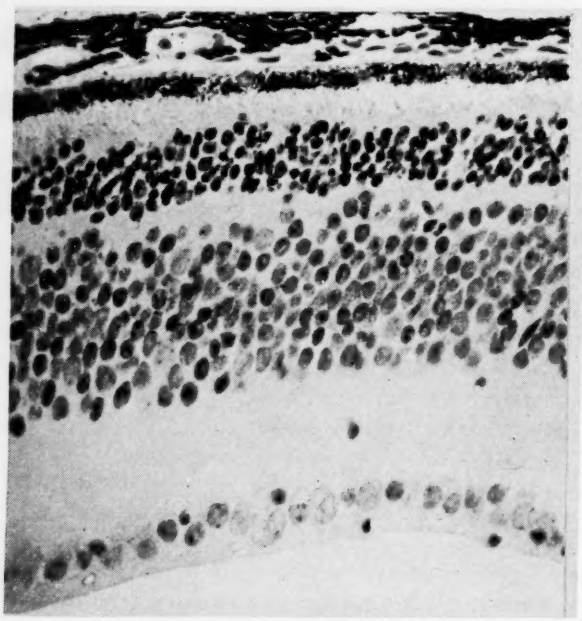

Figure 3. Dystrophic 14-day-old mouse retina. The abortive rod outer segments have just disappeared, judged by failure of staining with the periodic acid-Schiff method. The photoreceptor nuclei are disappearing. Compare with Figures 6 to 8, *in vitro*. 750X.

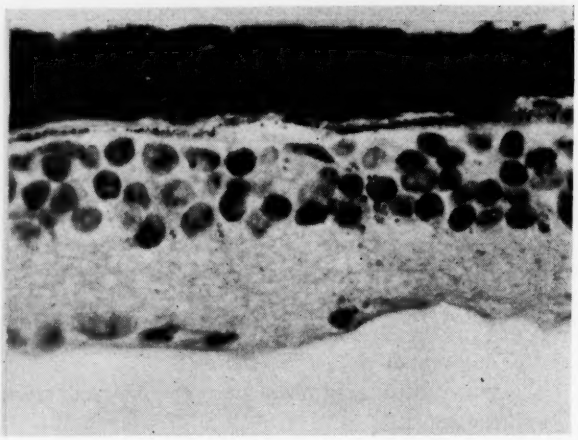

Figure 4. Dystrophic 2-year-old mouse retina. The photoreceptor cells are entirely absent. Occasional clusters of pigment granules are scattered through the retina. 1000X.

In media without added carotenoids, our results confirm those of Lucas and Trowell.[19] All three cell layers of the retina, as well as the pigment epithelium, chorioid, ciliary body, and iris remained in excellent health for more than a week *in vitro*. Retinal rod outer segments did not form. Usually, but not always, the retina showed necrosis of all layers at the posterior pole of the eye. The necrosis was already evident after 48 hours *in vitro* (Figure 5), and was not prevented by altering the position of the eye at the interface between the liquid medium and gaseous environment, or by changing the composition of the gas phase. The corneal epithelium usually was sloughed off, though the stroma looked healthy. The lens became opaque within 48 hours *in vitro*.

When all-*trans* vitamin A was added to the

*We are indebted to Professor George Wald and Mr. Paul K. Brown of the Harvard Biological Laboratories for generous gifts of 11-*cis* retinene, also called neo-b retinene.[3]

culture medium, the results were essentially the same. The retina appeared in good health, and rod outer segments were never seen. Fell[11] reported that excess all-*trans* vitamin A in the culture medium improves the growth of very immature embryonic chick retinas but does not alter the direction of histogenesis. In contrast, all-*trans* vitamin A has profound effects on histogenesis of many other organs *in vitro*.[11,21]

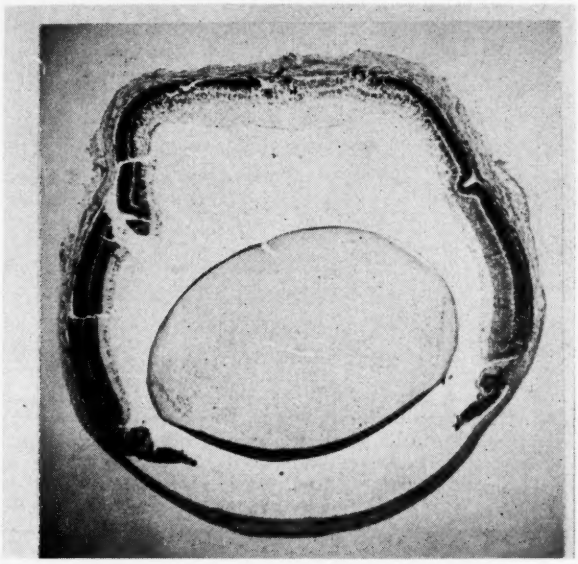

Figure 5. Normal 8-day-old mouse eye maintained 2 further days *in vitro*. The culture is in good health except for necrosis at the posterior pole. 50X.

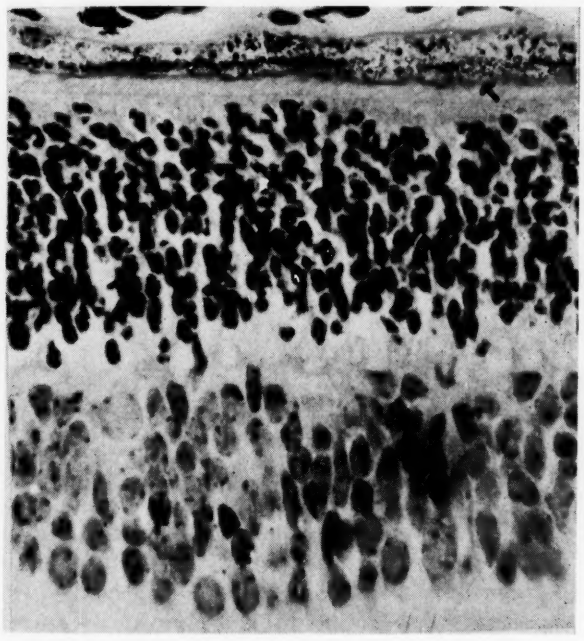

Figure 6. Normal 8-day-old mouse eye maintained 6 further days *in vitro*. Short rod outer segments (arrow) have formed in the presence of 11-*cis* retinene. Photoreceptor cell nuclei are differentiating normally. 1000X.

Results were dramatically different when 11-*cis* retinene was added to the culture medium. Further morphogenesis of retinal rod outer segments was regularly obtained. Short but definite rod outer segments were present in eyes of 6 to 9-day-old mice cultured for 2 to 6 days, and occasionally for 8 days. The outer segments in cultured eyes showed the same strong staining with the periodic acid-Schiff stain or with sudan black B as the outer segments in eyes which were not cultured. In fact, the periodic acid-Schiff method proved the most reliable, and perhaps the only certain indicator of the presence of rod outer segments, as distinct from distorted inner segments, pigment cell apical processes, or debris. In many specimens, whether fixed after a period in culture or taken directly from the mouse, the delicate rod zone swelled during histological processing, so that the individual rods appeared thinner and more elongated than they had been in life. Figure 6 illustrates the normal appearance and length typically attained by rod outer segments in the presence of 11-*cis* retinene *in vitro*.

Eyes of 10 and 11 day old mice already have short rod outer segments *in vivo*. When these eyes were cultured in the absence of 11-*cis* retinene, the outer segments vanished within 48 hours *in vitro*, as judged by examination of periodic acid-Schiff stained sections. In the presence of 11-*cis* retinene the outer segments were maintained or possibly were re-made.

Tissue Culture Studies on Potentially Dystrophic Eyes: Except for the retina, all parts of the eye behaved as described above for the eyes of normal mice. The retina showed three changes which distinguished them from retinas of normal mice *in vitro* (compare Figures 7 and 8). First, no rod outer segments were seen. Second, the number of photoreceptor nuclei decreased markedly and progressively *in vitro*. Third, the persisting photoreceptor nuclei showed a more immature pattern of nuclear chromatin. That is, the chromatin was segregated in several separate, sharply outlined granules or masses, whereas in retinas of normal animals of the same age the chromatin was usually disposed in one or two larger masses so that the nucleus had a more homogeneous appearance (Figures 7 and 8).

The development of dystrophic changes *in vitro* was previously obtained in the pioneering study of Lucas.[18] Our results with 11-*cis* retinene make the distinction between normal and dystrophic

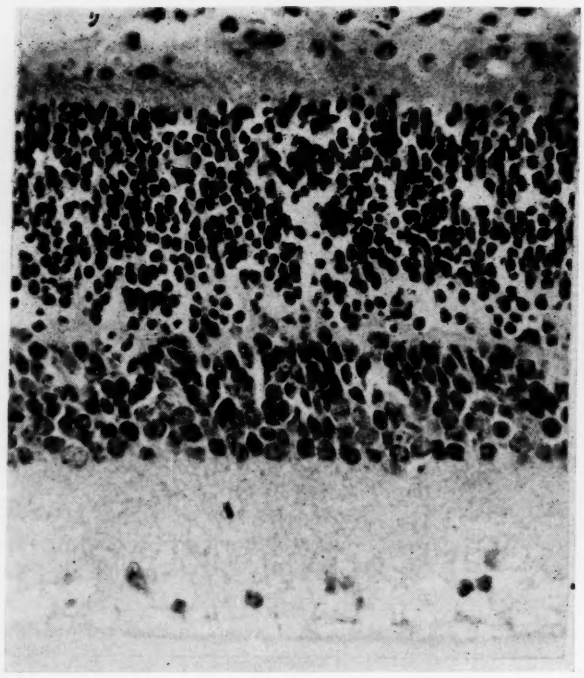

Figure 7. Normal 11-day-old mouse eye maintained 5 further days *in vitro*. Some photoreceptor cell nuclei are pycnotic and the nuclei are abnormally separated from each other, but most photoreceptor cells and bipolar cells are healthy. Short rod outer segments are present, though not easily resolved in the photograph. Compare with Figure 8, a specimen cultured in the same dish. 750X.

retinas *in vitro* more conclusive, since 11-*cis* retinene stimulates further differentiation of the normal retina while apparently having no influence on the progression of the disease in the dystrophic retina.

Discussion

The Facts Established in Vitro: In order to assess the value of a relatively untested tool like tissue culture for the study of disease, it is well to consider what the method has taught us about retinal dystrophy and what it has merely suggested. One fact and one further deduction seem valid: that all of the histologically recognizable features of the disease have been produced *in vitro*, and that the disease must be intrinsic to the eye. Thus, search for a circulating toxin, or therapy based on such considerations, would seem unpromising. Retinal dystrophy should be distinguished from diseases like human kernicterus or the Creeper fowl,[32] whose causes are in part extrinsic to the affected organ.

The possible role of 11-*cis* retinene in the retinal disease remains unsettled. The culture data suggest that 11-*cis* retinene has no influence on the course of the dystrophic process, but the culture method might be misleading in this matter. For example, the 11-*cis* retinene added to the culture medium on day 0 might become transformed to other substances, and not be available to the retina throughout the culture period. Other details of the culture technique and of the experimental protocols might similarly influence the data obtained. Negative results in tissue culture are rarely definitive.

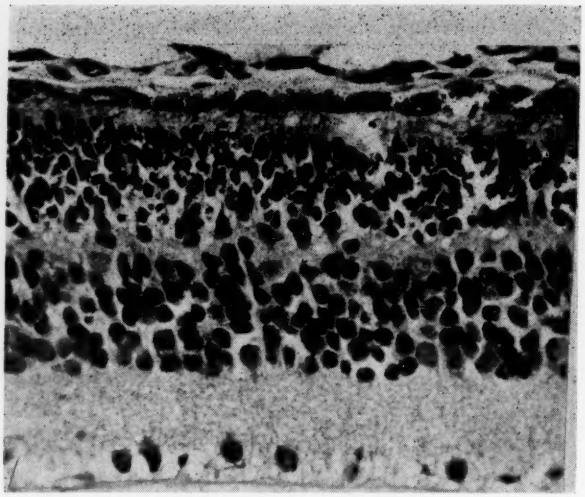

Figure 8. Dystrophic 11-day-old eye maintained 5 further days *in vitro*. Photoreceptor cell nuclei are disappearing and no rod outer segments are present, despite the 11-*cis* retinene added to the culture medium. The bipolar and ganglion cells are healthy. 750X.

Rhodopsin and Possible Causes of Retinal Dystrophy: A number of diseases are recognized which affect specialized cell parts late in development. Several of these (in addition to the retinal dystrophy) are available for experimental study as mutants in mice, including a developmental defect in myelin formation[14] and developmental failure in the inner ear.[5] Since more biochemical, physiological, and histological facts are available on the photoreceptor cells of the normal retina than on any other part of the nervous system, some speculations about the retinal dystrophy seem in order.

Rhodopsin is a photosensitive molecule composed of a carotenoid, 11-*cis* retinene and a protein, opsin.[30] It makes up a relatively high percentage of the dry weight of retinal rod outer segments, and is probably a structural component as well as the light-receiving pigment of the rods. The shape of the carotenoid molecule is of critical importance; only the 11-*cis* isomer of retinene can combine with opsin to make

rhodopsin. Clearly, if rhodopsin is a structural component of the rod outer segment, 11-*cis* retinene must be needed to build a rod in the first place.

In vivo the normal mouse eye converts all-*trans* vitamin A to 11-*cis* retinene. This isomer of retinene is made enzymatically from all-*trans* vitamin A by dehydrogenation and isomerization. In organ culture 11-*cis* retinene is not formed, even when the tissue is supplied with a massive excess of all-*trans* vitamin A. Yet the normal retina *in vitro* does make some outer segment material when provided directly with 11-*cis* retinene. (We are testing whether the normal eye in culture fails to dehydrogenate or to isomerize all-*trans* vitamin A.)

One theory about the disease is that retinal dystrophy might reflect a lack of availability of 11-*cis* retinene.[4] The culture experiments argue against this idea, for the disease develops even when 11-*cis* retinene is added to the culture medium. However, as discussed above, negative culture data on this point are not conclusive.

A more likely possibility is that the disease represents an inability to use 11-*cis* retinene, even if it is made by the eye or supplied from the outside. One reason for such a failure would be lack of opsin, the protein which binds 11-*cis* retinene to form[21] rhodopsin. However, without opsin, *no* outer segment should form and yet, a small outer segment does form. Some other reason for the inability to use 11-*cis* retinene must be sought.

Recent studies on retinal changes in rats deficient in vitamin A provide an important further clue. Dowling and Wald[7] correlated the histological deterioration of retinal rod outer segments with the disappearance of the protein opsin. They drew on earlier data that opsin is normally stabilized by its combination with retinene. If an eye is depleted of retinene the rod outer segments disappear, for a major structural protein of the outer segment has been rendered unstable.

A more severe retinal defect is obtained when rats are placed on a vitamin A-deficient diet supplemented with vitamin A acid, an analogue which serves the vitamin A requirements for all tissues but the retina.[8] Rats maintained for many months on this dietary regime remain in good general health, but show progressive loss of all parts of most retinal photoreceptor cells, and not merely loss of outer segments. As Dowling and Wald observed, these anatomical changes resemble inherited retinal dystrophy in animals, as well as human *retinitis pigmentosa*.

An Hypothesis Accounting for the Pathogenesis of Retinal Dystrophy: The genetic defect in retinal dystrophy might be manifested in the production of an opsin molecule of abnormal shape. This hypothesis categorizes retinal dystrophy as an error of protein synthesis, in common with other genetically determined diseases.[33] Also it accounts for all the known features of the disease. A rod outer segment begins to form, presumably with the abnormal opsin as a structural component. Because of its abnormal configuration the opsin would be unable to bind the specifically shaped vitamin A derivative, 11-*cis* retinene—even if the preformed retinene is provided directly *in vitro*. The opsin thus would not become stabilized and would break down. As opsin disappears, the rod outer segment breaks down.[7] Finally, the entire photoreceptor cell would degenerate. The only difference from the response to chronic vitamin A deficiency in the adult rodent[8] is a more rapid rate of cell loss in the immature animal with inherited retinal dystrophy.

On the other hand, the very wealth of available data on rhodopsin and its constituents may prove falsely attractive when one is theorizing about retinal dystrophy. The rod outer segment might prove not to be the site of primary expression of the disease, but merely one of the several parts of the cell affected by an as yet undefined disease process.

Role of Organ Culture in the Study of Disease: Although organ culture has been little explored as yet for the study of disease, some of its uses can already be recognized. It can help us to distinguish sources of disease extrinsic to a given organ from those which are intrinsic, as in the present study. Of the extrinsic sources, it can help in the search for a viral agent,[1] or in establishing the presence of an immunological mechanism.[2] Further, it may serve to screen possible therapeutic agents in those favorable instances where a disease can be reproduced *in vitro*. Some of the difficulties in applying organ culture for this purpose were noted above in discussing the "therapeutic failure" of 11-*cis* retinene in retinal dystrophy. However, the complexities are even greater *in vivo*, where a possible therapeutic agent may seem to be inert when in reality it has been diluted below threshold in the bloodstream, excreted, sequestered in some other organ, barred from entry, or chemically modified. Organ culture provides a unique opportunity to study disease processes in isolation from the complexities of the intact organism.

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Acute Intermittent Porphyria: Search for an Enzymatic Defect with Implications for Neurology and Psychiatry

LEWIS P. ROWLAND, M.D.

Introduction

Although it is a rare disease there has been great interest in acute intermittent porphyria for several reasons. First, the dramatic discoloration of the urine led to its early recognition as one of the original "inborn errors of metabolism" by Garrod.[49] Second, its clinical manifestations are also dramatic and are sufficiently varied that every medical student and physician must be aware of this condition in considering the differential diagnosis of many more common diseases. Third, hemoglobin, the cytochromes and several enzymes contain the porphyrin ring as prosthetic group; the biosynthesis of the porphyrins has been elucidated during the past two decades in the laboratories of Shemin,[150] Neuberger[53 54] and Rimington,[134] in one of the most impressive contributions of modern biochemistry.

For the same reasons, previous investigations of the disease have been carried out primarily by biochemists and physicians interested in pigment metabolism, rather than investigators whose interest is in the nervous system. But there is reason to believe that the pigmenturia is merely a visible by-product of the basic disorder; in this sense, the name of the disease is a misnomer.[178] Furthermore, peripheral neuropathy and mental disorder are outstanding manifestations of acute intermittent porphyria; the explanation of these symptoms would not only clarify this disease, but would also be relevant to the normal function of brain and nerve, and therefore to other neurological and psychiatric disorders as well.

There have been many recent reviews of both the clinical disorder and porphyrin metabolism;[38 60 61 84 100 106 134-136 146 150 180 185 187] the present discussion will be concerned primarily with neurological and psychiatric aspects of the disease, and with a possible enzymatic defect.

Clinical Aspects

INCIDENCE:

Because acute intermittent porphyria is an inherited disorder, it may be expected that certain geographical areas will have a greater number of cases than others (Table I). In South Africa, Dean and Barnes[29] have been able to trace most current cases to a single colonist who arrived there in 1688. In Scandinavia, Waldenström[180 181] has found that the incidence in different parts of Sweden varies from 1:1,000 to 1.5:100,000. Fennelly, et al.[41] have also observed local areas of increased incidence of the disease in Ireland.

In other parts of the world the disease seems to be rare. It is true that many cases are undiagnosed even in the best of hospitals. At such sophisticated centers as the National Hospital in London[38] and the Mount Sinai Hospital in New York,[156] the diagnosis is made less often than once a year. The disease is not recognized more frequently at the Columbia-Presbyterian Medical Center. There appears to be a slightly greater incidence among women than men, but the disease has been found in all geographic areas and racial groups. The great majority of symptomatic cases occur in young adults, but cases have been encountered in children[3 35 112] and in rare instances the onset of symptoms may be delayed until the eighth decade.[51]

INHERITANCE:

Several genetic surveys have indicated that the disease is inherited as a Mendelian dominan.[28 30 179] Exceptions to this are rare.[112] The advent of biochemical methods for the detection of porphobilinogen and delta-aminolevulinic acid in the urine[61 68 107] has substantiated the genetic studies of symptomatic cases and indicates that asymptomatic or latent cases occur.[73] The dis-

TABLE I

Geographical Variation in the Incidence of Acute Intermittent Porphyria

Area	Reference	Incidence of Acute Intermittent Porphyria
South Africa (European population)	29	1:100
Sweden	180, 181	1:1000
Ireland	41	1:80,000
Leeds	6	1:60,000
Australia	140	1.5:100,000

From Department of Neurology, College of Physicians and Surgeons, Columbia University, New York; Scholar, Sister Elizabeth Kenny Foundation.

ease has been concordant in two sets of twins.[85 180]

SYMPTOMS AND SIGNS:

The major symptoms may be divided into three groups: gastrointestinal, neural and psychiatric. The relative frequency with which specific symptoms have been encountered in different series is indicated in Table II.

Gastrointestinal Symptoms: Abdominal pain, usually associated with vomiting or constipation, is the most frequent symptom and attacks occur at some time in almost every case. The symptoms may occur alone or in association with neurological or psychiatric manifestations. The pain may be very severe and abdominal tenderness may be present[61] but serious abdominal rigidity is lacking. The duration and precise location of the pain vary but fever and leucocytosis occur in some attacks and simulation of an acute surgical emergency may be virtual. Many patients have been subject to unnecessary laparotomy for this reason and the warning to surgeons has been repeated many times.[20 105 180] The occasional presence of true intra-abdominal surgical emergencies in patients with acute porphyria[85 113 190] complicates the problem of differential diagnosis, however.

Neuropathy: Symptoms due to neuropathy occur at some time in about two-thirds of the cases. The neuropathy does not differ from the polyneuritis of many other disorders, and the limbs are usually affected in more or less symmetrical fashion. Usually there is a flaccid quadriparesis; at times the legs are more severely affected than the arms, but it is very unusual for the arms to be affected without simultaneous involvement of the legs.

Sometimes muscular wasting is prominent,[32 139] and electrical study of the muscles shows appropriate evidence of denervation.[121] In severe attacks, the lower cranial nerves may be affected and many of the cases progressing to this extent have been fatal.[105] Respiratory paralysis is the greatest threat to life and has been responsible for most of the fatalities due to acute intermittent porphyria. No matter how severe the paralysis, however, recovery may follow,[79 105 121] and several patients have survived periods in a mechanical respirator.[35 76 140] Some survivors have had serious permanent disability but others have had no functional deficit.

The motor disorder usually dominates and in some cases there is no sensory deficit at all, but it is likely that some acral loss of cutaneous sensation or proprioceptive deficit in the legs is more common than has been reported. Pain in the limbs and tenderness of the muscles are common even when overt signs are lacking.

It is stated that asymmetrical paresis[178] and variation in both paresis and reflexes[105 137] should not be regarded as unusual. Paralysis uncommonly occurs in patients who have not had previous attacks of abdominal pain.

It is noteworthy that the cerebrospinal fluid is almost always normal during attacks of paralysis; in one case marked elevation of cerebrospinal fluid protein[7] and in another pleocytosis[101] were reported, but in the first of these porphobilinogen was not demonstrated in the urine, and the second was atypical in other respects as well (see page 24). Moderate elevation of cerebrospinal fluid protein concentration has been reported in a few cases.[127 164] Values greater than 100 mg.% may occur[77] but this is such a rare event that even when porphobilinogen is present in the urine of a patient with polyneuritis, marked elevation of the cerebrospinal fluid protein concentration may be taken to indicate the presence of an independent process.[123]

Cerebral Disorders: Many patients with acute

TABLE II

Clinical Manifestations of Acute Intermittent Porphyria

	Waldenström 233 Cases (Ref. 180) %	Markowitz 69 Cases (Ref. 105) %	Goldberg 50 Cases (Ref. 61) %
Abdominal Pain	85	95	90
Vomiting	59	52	75
Constipation	48	46	70
Diarrhea	9	11	10
Abdominal Surgery	22	46	–
Paresis	42	72	66
Muscle Pain	–	53	–
Convulsions	10	–	16
Sensory Loss	9	24	38
Transient Amaurosis	4	–	6
Diplobia	3	–	–
Delirium	28	52	18
Hysteria, Depression	27	26	28
Psychosis	–		12
Hypertension	40	49	55
Tachycardia	28	51	60
Pigmentation	7	13	16
Fever	37	36	12
Azotemia	10	27	6
Jaundice	3	–	0

intermittent porphyria do not have serious personality disorders except during an attack. But Roth[137 138] has suggested that there is frequently a life-long pattern of neurotic behavior and Kark[84] has used the word "termagantism" to describe the "mental agitation which may persist in remissions." This unpleasant behavior and the ill-defined nature of the abdominal pain have frequently led competent psychiatrists to consider patients hysterical, a diagnosis which may be erroneously supported by the occasional improvement of limb paresis after suggestion.[37 78]

Some patients may seem psychotically depressed, or hallucinations may lead to the diagnosis of schizophrenia, and many patients have been institutionalized. In acute attacks, especially in combination with neuropathy, the mental aberration is apt to be that of an organic mental syndrome, and this may be transient. Occasionally the organic mental syndrome may progress to coma,[37 85] which may also be transient. Recently it has been suggested that emotional factors may precipitate an acute episode of pain or paralysis.[103 119]

As indicated in Table II, more than 10% of patients have seizures. These usually occur during an acute attack, and status epilepticus may ensue; recurrent seizures over many years are less common but have been recorded.[20 120 137] The convulsions are usually generalized but may be focal. There are no characteristic electroencephalographic abnormalities.

In contrast with the frequency of disorders of mentation and seizures is the absence of evidence of other kinds of central nervous system injury. A few cases have been reported in which Babinski signs were observed[61 77 155] but this is unusual. Clear evidence of myelopathy was said to be present in one of Goldberg's cases[61] but has not been described by others. Transient blurring of vision or amblyopia has been reported several times,[60 61 106 138 156 178 180] but the pathogenesis of this symptom is not known. Focal cerebral symptoms have not been clearly described in any well-documented case report; e.g., in one case of cerebral blindness,[66] and another of hemianopia,[106] there was no porphobilinogen in the urine (see page 24). In another case,[113] a transient hemiparesis could have been due to independent vascular insufficiency.

Other Symptoms: Elevation of the blood pressure during an acute attack, with subsequent return to normal in those patients who recovered, were found in more than half of Goldberg's cases.[60] Persistent hypertension may occur,[141] but is not clearly related to the disease. Hypertensive encephalopathy has not been reported.

Pigmentation of the skin was present in 7-16% of the series summarized in Table II but photosensitivity does not occur in typical cases. There is no evidence that hepatic, renal or cardiac damage is an integral part of the disease, although these organs may be involved in some cases.

ROLE OF BARBITURATES:

In South Africa, Dean and Barnes[29] state that all attacks of paralysis have been precipitated by the administration of barbiturates. Many attacks in patients elsewhere have not been related to these drugs, but in a great many of the recorded cases of paralysis, the administration of barbiturates has seemed to be dramatically deleterious.[1 6 20 50 51 61 77 79 83 105 113 120 178 193] These drugs have usually been given for psychiatric reasons or because of abdominal pain; less frequently the drugs were given to control seizures, insomnia or hypertension. Subsequently paralysis ensued. The number of cases recorded in which this sequence has occurred is impressive, but the symptoms for which the drugs were prescribed indicate that the attack had already begun prior to the administration of the barbiturate, and the subsequent development of paralysis might be considered fortuitous. In a few patients, barbiturates were used as anticonvulsants without clear-cut evidence of subsequent deterioration, but also without definite proof that they had been given with impunity.[33 37 105 172]

There is additional evidence that there is a causal relationship between drugs and symptoms, however. Attacks have been precipitated in previous asymptomatic individuals by barbiturates.[83] Furthermore, the biochemical abnormalities of the disease can be reproduced in rabbits, rats and chick embryos[22 56 63 95 143 163 167 168] by certain barbiturates, especially allylisopropylacetylcarbamide and allylisopropylacetamide. However, the experimental disease may not mimic exactly the human disorder in that paralysis has not been clearly demonstrated in rabbits,[42 63] although it has been reported in rats.[22] In a survey of human barbiturate addicts[84] only 2 of 100 subjects excreted porphobilinogen in the urine and few abnormalities were found among individuals who had taken large amounts in suicidal attempts;[195] this may be only a reflection of the abnormal sensitivity of patients with porphyria to barbiturates in contrast with normal individuals.

Goldberg[60 61] suggests that barbiturates may be important in two ways: 1) Prolonged administration to asymptomatic individuals may provoke an attack, and 2) Administration of bar-

biturates during an acute attack may precipitate paralysis.

COURSE, PROGNOSIS AND TREATMENT:

The course of acute intermittent porphyria covers all conceivable variations. Some patients are asymptomatic. Some develop a typical attack for the first time at age 70. Some have repeated episodes of abdominal pain, or personality alteration, mild or severe, for many years. Paralytic attacks are apt to be more explosive, with symptoms developing within a few days or weeks, and leading to fatal issue, arrest, or recovery within a period of a few weeks. Periods of improvement and relapse may occur for several years but separate distinct episodes of paralysis after complete recovery are unusual.[9] In patients who survive, improvement may continue for several years, and among survivors, neither severe psychiatric disorder, coma, nor extensive paralysis[35 36 65] precludes satisfactory recovery. It is clear, however, that paralysis is the major threat to life.

The extreme variability of outcome of individual attacks makes evaluation of drug therapy difficult. Two recent additions to the long list of remedies for which success has been claimed are steroids and chlorpromazine,[109 111] but both have been given to some patients without effect.[51 61 81 105 149 156] Similar reservations apply to the evaluation of metal-chelating agents.[122] Dramatic improvement may occur without specific treatment[45] and there is no uniformly successful therapeutic agent.

A cardinal rule in the management of patients with intermittent porphyria is avoidance of barbiturates. Phenothiazine drugs can be used for appropriate psychiatric indications, chloral hydrate and paraldehyde for sedation, paraldehyde for control of status epilepticus, hydantoins for treatment of chronic convulsive disorders, and meperidine for pain. Non-barbiturate anesthetics should be used for surgical procedures. Symptomatic treatment of paralytic episodes, including tracheotomy, mechanical methods of artificial respiration[35] and appropriate physical medicine procedures, may not only be life-saving but can minimize subsequent disability. Electroshock therapy has been of apparent benefit in some cases[44 96 118] but not in others.[98 105]

Attacks may be precipitated by infection or other intercurrent illness.[60] The effect of pregnancy has been unpredictable, but there have been several patients in whom deterioration during or immediately after pregnancy has been marked,[60 61 81] so that therapeutic abortion is sometimes justified. In some women attacks may coincide with menstrual periods[61 177] and increased excretion of porphobilinogen has been reported to occur at that time.[86] Surgery[60 61] and spinal anesthesia[25 137] have also seemed to provoke attacks. In addition to barbiturates, sulfonamides,[1 98 105 116 133] alcohol[21 166 178] and other drugs[26 105] have been indicted.

PATHOLOGY:

Schwartz and Moulton[147] have provided a comprehensive review of the autopsy findings in cases reported prior to 1954 and there have been additional pathological surveys.[50 77] There is no pathognomonic histological lesion in acute intermittent porphyria and there is no consistent pathology outside the nervous system. Even in patients dying of paralysis the nervous system may appear normal[128 137 147] so that the fundamental lesion seems to be metabolic. This concept is supported by the paucity of lesions in the cerebrum in patients with mental symptoms. In most patients, however, clinical evidence of neuropathy is attended by demyelination of peripheral nerves, sometimes with axonal degeneration as well.[50 77 147] Changes in the anterior horn cells are usually interpreted as being due to retrograde degeneration owing to the periopheral neuropathy; sometimes, however, the neuronal damage seems disproportionately great[50 77] and primary insult to these cells has not been excluded.[77]

Elsewhere in the central nervous system, lesions have been few and generally inconspicuous; although cerebral and cerebellar demyelination has been reported this has not been severe and minimal demyelination of the cord was present in only 5 of 41 cases examined.[147] Purkinje cell degeneration is not attended by clinical evidence of cerebellar dysfunction and diffuse neuronal disease throughout the hemispheres may occur, but the type, degree and location of the cerebral pathology has been variable.[147] Gross vascular lesions are unusual and although a vascular basis for the neural disorder has been suggested,[31] neither the histological nor the clinical picture are now thought to support this; most recent authors believe the non-specific histological changes to be most compatible with "toxic" or "metabolic" events.[50 77 147]

BIOCHEMICAL ABNORMALITIES:

For many years acute intermittent porphyria was identified by the clinical picture associated with the excretion of red urine. The color was found to be due to the excretion of abnormal amounts of uroporphyrin and subsequently there

was debate as to the particular porphyrin isomer involved.

The difference of opinion has continued until the present[188] but Rimington[136] and Gray[70] suggest that the argument has largely lost its significance since the most important pathological excretory product is probably not porphyrin, but its precursor, porphobilinogen.

In 1931 Sachs[139] found that there was a substance in the urine which reacted with dimethylaminobenzaldehyde (Ehrlich's Reagent) but, unlike the product of this reagent with urobilinogen, this compound could not be extracted by chloroform. The importance of this colorless precursor of porphyrins was subsequently emphasized by Waldenström[177 181 182] who named it porphobilinogen. In 1941 Watson and Schwartz[189] devised a simple clinical test to demonstrate the presence of this substance and it was isolated from the urine of a patient by Westall in 1952.[191] Cookson and Rimington[24] elucidated its structure in 1954. It has been shown that porphobilinogen can be converted into porphyrins of either I or III series (v.i.) non-enzymatically.[24] This explains why freshly voided urine in porphyria may not only be colorless, but may actually be devoid of porphyrins;[185] upon standing, or after heating in acid, porphyrins will be formed.[16 24 55 127 128]

Porphobilinogen is excreted in small amounts in normal urine,[107] but the Watson-Schwartz test is virtually pathognomonic of porphyria.[75] False positive reactions are rarely encountered[184] and doubt may be cast upon the diagnosis if this test for porphobilinogen is not positive during an acute attack. (In cases which are reported to demonstrate some atypical phenomenon the qualitative test for porphobilinogen should be supported by demonstration of the characteristic spectral absorption pattern of the compound formed with Ehrlich's reagent and also by paper chromatography.) Most patients continue to excrete porphobilinogen even after the acute attack subsides, although frequently in lesser amount. In some patients the excretion of porphobilinogen ceases entirely between attacks. At autopsy porphobilinogen is found in large amounts in liver, kidney and myocardium[69 127 145] but there is no excessive deposition of porphyrins.[50 51 69 90 145]

The development of chromatographic methods has also allowed the demonstration that the precursor of porphobilinogen, delta-aminolevulinic acid, is also present in the urine normally but is increased in most patients with porphyria.[68 73]

These biochemical abnormalities can be reproduced in rabbits and mice by the administration of allylisopropylcarbamide or allylisopropylacetamide.

It has been said that unlike the human disease delta-aminolevulinic acid is not excreted in experimental porphyria[162] but recently excessive amounts of this compound have been found in the liver of experimental disease.[131] Aminoaciduria occurs in both the experimental[63] and human disease[108] and can be interpreted as a secondary phenomenon. If there is a disorder in tryptophan metabolism[126] it may be in the same category.

DIAGNOSIS:

Other Forms of Porphyria: Acute intermittent porphyria has to be differentiated from other forms of porphyria. No classification is entirely satisfactory but the following criteria provide a useful division as indicated in Table III. Congenital porphyria differs from intermittent porphyria clinically and biochemically. Symptoms start at birth. Photosensitivity and deforming skin lesions (hydroa aestivale) are prominent and the extensive deposition of por-

TABLE III

Clinical and Biochemical Features of the Porphyrias

	Congenital Porphyria	Acute Intermittent Porphyria	Porphyria Cutanea Tarda	Mixed Variety
Inheritance	Recessive	Dominant	—	—
% Male	50	35	75	—
Age at Onset	Birth	After adolescence	Adult	Adult
Photosensitivity	+	0	+	+
Skin Lesions	+	0	+	+
Erythrodontia	+	0	0	0
Hemolytic Anemia	+	0	0	0
Abdominal Pain	0	+	0	+
Neuropathy	0	+	0	+
Psychosis	0	+	0	+
Hepatic Disease	0	0	+	±
Urinary Porphyrin	URO I	URO III and I	URO III	URO III
Fecal Porphyrin	—	—	+	+
Porphobilinogen	0	+++	±	++

phyrins in body tissues leads to erythrodontia and discoloration of bones. Hemolytic anemia also occurs. The urinary porphyrin is uroporphyrin I and porphobilinogenuria does not occur, nor do the neural, psychiatric and abdominal symptoms appear.

Porphyria cutanea tarda, in its pure form, starts in adult life, occurs most frequently in males, and is characterized by skin lesions, photosensitivity, and, frequently, hepatic disease. The urinary porphyrin is uroporphyrin III; Rimington and his colleagues[80 104] have indicated that fecal excretion of porphyrin in clinical remissions may be characteristic. Porphyrins may be deposited in the liver and other organs, but not in neural tissues.

Mixed forms have to be included because in South Africa[29] and rarely elsewhere[116] otherwise characteristic acute porphyria may be accompanied by photosensitivity, and in some patients with porphyria cutanea tarda[19 34 43 69] attacks of abdominal pain, paralysis, or mental disorder, not ordinarily seen in this category, may occur; when they do, porphobilinogenuria is usually present.[17 19 34 104] Rarely, different forms of the disorders may appear in the same family.[21] Additional problems of classification are caused by reports of patients with paralysis but no porphobilinogenuria[106 124] but this compound is unstable in acid solutions and the test may be negative if the urine is allowed to stand.[30 145]

Watson and his colleagues[145 187] classify the congenital form as erythroporetic porphyria and include all other varieties as hepatic porphyria, implying a common basis for both acute intermittent porphyria and porphyria cutanea tarda. Rimington,[80 104] however, believes the latter two are each due to a different metabolic abnormality. Dean and Barnes[30] believe the form encountered in South Africa is biochemically different from that in Sweden. These differences of opinion will only be resolved when the specific enzymatic defects are proven.

Other Forms of Porphyrinuria: Excessive excretion of urinary porphyrins may occur in a variety of other diseases,[187] but rarely in amounts comparable to the porphyrias, and rarely in amounts sufficient to color the urine. Lead poisoning is the most important of these because the neuropathy and psychosis may mimic that of acute porphyria and because delta-aminolevulinic acid may be present in the urine,[72 74 170] although porphobilinogen[9 74] ordinarily is not. In some patients occupational exposure to lead may have precipitated attacks of acute porphyria.[46 149]

Other Forms of Pigmenturia: The color of red urine may be due to the presence of hemoglobin or myoglobin as well as porphyrins. Hematuria is identified by microscopic examination. Hemoglobinuria is identified by reaction with guaiac or benzidine (porphyrins do not give this test) and the serum is also discolored. Myoglobin also gives a positive guaiac or benzidine test, but the serum is clear and it can be differentiated from hemoglobin spectrophotometrically, electrophoretically on paper, or by solubility characteristics.

Other Diseases: The most common diagnostic errors are to regard patients with acute intermittent porphyria as having acute surgical emergencies or hysteria, or to fail to characterize the polyneuritis more specifically. The latter is one of the hazards of using the term "Guillain-Barré Syndrome" as a specific diagnostic term. Because clinical evidence alone will not differentiate these conditions from porphyria, and because the color of the urine may be normal in porphyria, the proper diagnosis must be considered and the Watson-Schwartz test performed. This test is so simple, convenient and reliable that this test should be part of the routine urinalysis in all patients.[65] Only in this way will diagnostic errors be avoided. Furthermore, asymptomatic cases will be discovered and appropriate precautions regarding barbiturates can then be taken. The discovery of asymptomatic and atypical cases would also serve to make statistics regarding the incidence of the disease more meaningful and would permit a more realistic picture of the natural history of the disease.

The Biochemical Lesion

PORPHYRIN TERMINOLOGY

The terminology of porphyrin structures is that developed by Fischer (Fig. 1). The basic tetrapyrrole structure, with no side groups, is porphin. In the uroporphyrins, there are two side-chains, acetic ($-CH_2COOH$) and proprionic ($-CH_2CH_2COOH$). Depending upon the positions of these side-chains, there are four possible isomers, but only two are found in nature: in the I series, the acetic and proprionic groups alternate regularly, while in the III series, the order is reversed on ring D. Decarboxylation of the acetic residues, to form a methyl group, converts the uroporphyrin to coproporphyrin. If the proprionic residues on rings A and B are decarboxylated and dehydrogenated to vinyl groups, the structure is now protoporphyrin IX. (There are three side-groups in protoporphyrin, allowing 15 isomers, but it is protoporphyrin IX which

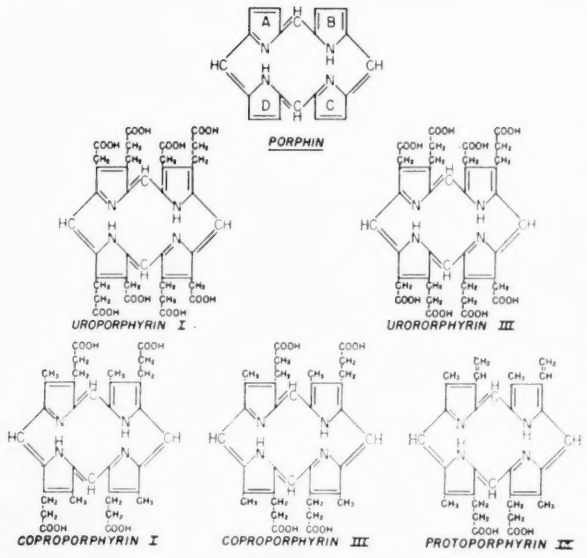

Figure 1.

is the porphyrin moiety of haem, myoglobin, the cytochromes and chlorophyll.) At one time, "hematoporphyrinuria" was the term used for the various disorders, but hematoporphyrin is a synthetic compound which has not yet been found to occur naturally.

BIOSYNTHESIS OF PORPHYRIN

The major steps in the biosynthesis of porphyrines are outlined in Figure 2. Glycine and succinyl coenzyme A are condensed to form delta-aminolevulinic acid (ALAC) under the influence of the enzyme, ALAC-synthetase. The formation of the postulated intermediate, α-amino-β-ketoadipic acid, has not been demonstrated since it is very unstable and decarboxylates spontaneously; only one enzyme seems to be involved in this conversion.[88] The enzyme is present in nucleated erythrocytes of lower animals; it is present in reticulocytes, but not in mature mammalian erythrocytes. This difference may be attributed to the fact that the enzyme is bound to mitochondria. ALAC synthesis has also been demonstrated in other mammalian tissues, especially liver and kidney.

The condensation of two molecules of ALAC to form porphobilinogen is mediated by ALAC-dehydrase. Liver and kidney are rich sources of this enzyme, and it has also been demonstrated in mature human erythrocytes. The formation of the tetrapyrrole from porphobilinogen is still under investigation but considerable progress has been made in elucidating the enzymatic steps.[15 99 197] It can be seen that four molecules of porphobilinogen could combine without modification of the side chains to form uroporphyrin. The intermediate steps involve compounds in which the methene bridge groups are present in reduced form, the uroporphyrinogens.

In addition to its role as a precursor of porphobilinogen, Shemin[150] and his associates have shown that the delta carbon of ALAC may contribute to the "one-carbon pool." When ALAC-5-C^{14} was administered to ducks, the label was found in the positions labeled by other one carbon sources—formate, positions 2 and 8 of adenine, methyl groups of methionine, and the beta carbon of serine.[114 150] Furthermore when ALAC-1,4-C^{14} was administered, the label was found in succinic acid.[114] When ALAC-1,4-C^{14} is administered to normal man, the expired carbon dioxide is labeled.[12] These findings could be explained by the series of reactions depicted in Figure 3.

When ALAC is incubated with α-ketoglutaric acid in the presence of a source of enzyme, transamination apparently occurs, and glutamic acid can be identified as a product. This enzyme, ALAC-transaminase, has been found in mammalian tissues[92] and C. diphtheriae,[8] but whether it is a major route to α-ketoglutaraldehyde has not been determined. Indeed, α-ketoglutaraldehyde has not yet been identified as a naturally-occurring biological substance, but Nemeth and Shemin[114] showed that it can give rise to suc-

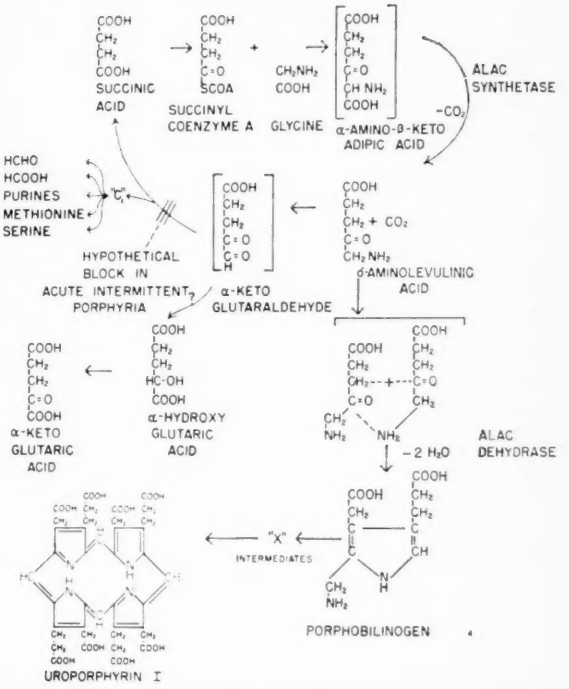

Figure 2.

cinic acid and a one-carbon unit. (It had previously been shown that α-ketoglutaraldehyde may be converted to α-hydroxyglutaric acid by yeast[117] and E. coli.[174]) It is possible that this route is a major pathway for the contribution of the alpha carbon of glycine to the one-carbon pool, but for at least one reaction (methionine biosynthesis) in one organism, ALAC could not substitute for glycine.[194]

This alternate pathway may be an important mechanism for the control of ALAC metabolism and heme formation. Rhodopseudomonas spheroides may be regarded as an organism which, when grown anaerobically, has "microbiological acute porphyria."[88] That is, under these conditions it excretes into the medium porphobilinogen, ALAC and coproporphyrin. When grown aerobically, however, these products do not accumulate. Cell-free extracts of anaerobically grown organism are rich sources of ALAC-synthetase, whereas this enzyme is diminished in extracts of cells grown aerobically.

PATHOGENESIS OF ACUTE INTERMITTENT PORPHYRIA

One current theory of the pathogenesis of acute porphyria does not implicate the metabolic pathways of porphyrin biosynthesis. The apparent therapeutic efficiency of metal-chelating compounds has led to the hypothesis that the primary defect is heavy metal accumulation and that the excretion of porphyrins, bound as they may be to zinc, is a phenomenon secondary to the metal excretion.[122] This theory seems erroneous for a variety of reasons; 1) The excretion of porphyrins is not the crucial biochemical abnormality; 2) The theory does not explain the accumulation of ALAC and porphobilinogen; 3) The fundamental premise of the argument has not been proven, since the drugs are not uniformly successful[122] and may even precipitate an attack;[47] 4) Hepatic zinc was actually measured in one fatal case and was normal;[115] 5) If chelating agents do have therapeutic value, this might be due to effects on enzymes, such as ALAC-synthetase[54] or ALAC-dehydrase,[53] or others. The complex effects of chelating agents is illustrated by ALAC-dehydrase.[53] Dimercaptopropanol (BAL) enhances the activity of this enzyme, presumably by protecting sulfhydryl groups, but the enzyme is inhibited by ethylenediaminetetra-acetate (Versene). Another chelating agent, penicillamine, is a powerful inhibitor of ALAC-synthetase.[54]

Most theories have implicated the pathways of porphyrin biosynthesis in one way or another. It was originally thought that the symptoms of acute porphyria could be explained by the pharmacological effects of porphyrins.[4] Free porphyrins are found in the nervous system[14 23 89-91 159 160] and the remarkable affinity of porphyrin compounds for myelin has been made the basis of a specific histological stain[92] as well as a method for identifying lipids on paper chromatograms.[165] But the function of the free porphyrins in the nervous system is not known, none of the symptoms of acute porphyria occur in congenital porphyria, in which there are large amounts of circulating porphyrins, and the parenteral administration of uroporphyrin[62] or coproporphyrin[187] does not cause any symptoms except photosensitivity. In acute porphyria no deposition of porphyrins has been found in the brain or nerves.[50 90]

The accumulation of porphobilinogen could be explained by a block in conversion of this compound to porphyrin. If this were so, there ought to be a deficiency of hemoglobin, which is not the case. In Sedormid-induced porphyria in rabbits, there is a diminution in the activity of a porphyrin-enzyme, liver catalase[142-144] which is compatible with this theory, but in a single human case in which this enzyme was studied, liver catalase activity was normal, and so were the concentrations of myoglobin and cytochromes in muscle.[69] The latter compounds were also normal in Sedormid porphyria. Furthermore, porphobilinogen is excreted rapidly by the kidneys, so that high levels in the plasma are not ordinarily found,[57 63] and it is pharmacologically inert.[62] In one case, porphobilinogen was found in liver, kidney and heart, but not in the brain.[158] In Sedormid-porphyria, there is no block in the conversion of porphobilinogen to porphyrin.[110] ALAC also has no perceptible pharmacological action, except that it causes photosensitivity.[11 12 82 148] In the light of these findings it seems very unlikely that there is a block along the main pathway from ALAC to porphyrins.

Other possibilities must therefore be considered. It has been postulated[60 61] that porphobilinogen is utilized for some other pyrrolic compound, which like vitamin B_{12}, is necessary for the normal maintenance of myelin, and that this pathway is blocked. This could explain the biochemical abnormalities, but it remains purely hypothetical since there is no evidence that porphobilinogen is utilized for anything but porphyrin synthesis.

One other possibility remains, namely, a block in the alternate pathway for the utilization of

ALAC. This could be in either of two steps, the conversion of ALAC to α-ketoglutaraldehyde, or the conversion of the latter to succinate and the one-carbon fragment. There is no direct evidence for either of these, since suitable assays for these enzymes have not yet been developed, but all of the evidence cited above could be explained by an enzymatic block of this pathway.

Additional indirect evidence supports this concept: 1) In experimental porphyria, in rabbits given Sedormid, direct assay of hepatic ALAC-dehydrase has shown the activity to be greatly enhanced.[52 87] In one patient with acute porphyria, Kellerhals[87] found abnormally increased activity of the enzyme in hemolyzed blood; 2) In humans with congenital or cutaneous porphyria the conversion of ALAC to porphobilinogen as studied with isotopic compounds[11 12 148] is normal, but in acute intermittent porphyria about three times as much of the label was incorporated into porphobilinogen. In these studies by Berlin, Scott and Neuberger,[11 12] it was also found that the isotope was diluted to a greater extent in porphyria, implying the presence of large pool of endogenous porphobilinogen; 3) After the oral administration of glycine by Richards and Scott,[132] the rate of excretion of ALAC was increased in 7 of 9 patients with acute porphyria, but there was no change in normal individuals. After the administration of glycine, the plasma level of serine increases in normal individuals, presumably by way of the one-carbon unit from delta-aminolevulinic acid. In 3 of 6 patients with acute porphyria this rise in serine was much diminished, which is consistent with the hypothesis proposed. The fact that 3 patients showed a normal rise, is not necessarily inconsistent with the hypothesis because there may be other mechanisms which permit the conversion of the alpha carbon of glycine to the one-carbon pool;[194] 4) In chick embryos treated with either Sedormid or allylisopropyl acetamide, there is enhanced excretion of porphobilinogen and coproprophyrin. Concomitantly, there is diminished excretion of uric acid[94 169] and incorporation of glycine-2-C^{14} into uric acid[95] is diminished.

On the basis of the latter findings, Aldrich and his colleagues[3] postulated that the pathogenesis of symptoms is due to decreased formation of purines because of the block in the contribution of ALAC to the one-carbon pool. This may be so, but there are many other sources of one-carbon fragments, which could compensate for the defective contribution from ALAC.

The alternative hypothesis, which seems most promising, is that the block is in the further metabolism of α-ketoglutaraldehyde, with accumulation of this keto-aldehyde. Compounds of this category are known to be toxic[129] (because of reactions with thiols, aminoacids, ketoacids and several enzymes), but this particular substance has not been tested for its pharmacological effects, and its effects on neural metabolism are not known. The relationship of the metabolic fault to the symptoms of the disease will still have to be explained once the biochemical lesion is known. The long period of asymptomatic latency, the intermittent nature of symptoms, and the role of exogenous factors in precipitating attacks will also have to be explained.

It can be seen that all arguments regarding the enzymatic defect in acute intermittent porphyria are hypothetical, but the tools for appropriate analysis are available and it may be expected that within the next few years, acute intermittent porphyria will join the growing list of hereditary metabolic errors in which the specific enzymatic defect is known.

Summary

1. Acute intermittent porphyria is an inherited disorder in which the enzymatic defect results in peripheral neuropathy, mental symptoms and convulsions. Elucidation of the nature of this defect would yield information regarding the normal function of brain and nerve, and also about other diseases affecting these structures.

2. The essential biochemical abnormality is not the urinary excretion of porphyrins, but the excessive formation and urinary excretion of porphobilinogen and its precursor, delta-aminolevulinic acid.

3. Delta-aminolevulinic acid, besides its role as a precursor of porphobilinogen and porphyrins, is normally converted to succinic acid and a one-carbon unit. A defect in this alternate pathway could explain the known biochemical abnormalities, and would explain the experimental findings in both human porphyria and the drug-induced disorder in animals, but direct proof for this hypothesis has not yet been provided. Other theories have been proposed to explain the pathogenesis of this disorder but are deficient in one respect or another.

4. Any theory of the pathogenesis will have to explain the relationship between the biochemical lesion and the symptoms, the long latent period prior to the onset of symptoms in adult life, the intermittent nature of symptoms and the role of exogenous factors, such as barbiturates.

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The Thyroid: Genetic and Psychiatric Relations

SIDNEY C. WERNER, M.D.

It is planned in this presentation to outline the growing evidence for genetic and nervous influences upon the thyroid and to discuss the effects of thyroid hormone upon the nervous system. The discussion will of necessity include both health and disease of the gland.

Physiology

The normal human thyroid is a small organ weighing about 25 grams. It lies unobtrusively astride the trachea in the lower neck where it is fed by a generous blood supply. This latter fact suggests that the gland has a considerable capacity for varying its functional activity and also that the result of the gland's activity is important to the economy of the body as a whole. Both suggestions have been amply confirmed in health and disease.

Although apparently the sole functions of the gland are to convert inorganic iodine to organic hormone and to release this product to the blood stream, the effect of the hormone, or of its metabolic products, influences every cell in the body.[1] Conversely, the thyroid is a part of the body and is affected by regulatory mechanisms and by events common to the body as a whole.

The observation of Baumann in 1896[2] that the thyroid selectively concentrates iodine, opened the way to modern investigation of the gland. The subsequent identification of thyroxine within the gland and of its chemical structure[3] then seemed to settle the question of the identity of the thyroid hormone. With the introduction of radioiodine and the popularization of paper chromatographic methods of separation of the iodoaminacids, however, it becomes apparent that there were two substances with thyroid hormone activity, l-thyroxine (T4), with four iodine atoms and a substance with three iodine atoms, l-triiodothyronine (T3), which has four to five times the potency of T4, and which was found only in small concentration in the thyroid proper or in the blood.[4]

The physiological dilemma created by the high potency but low concentrations of T3 led to the ingenious theory that T4 is the transport form of the thyroid hormone to the tissues and that T3 is the active form produced in the tissues by deiodination of T4. Some secretion of T3 by the thyroid, some production of diiodothyronine (T2), and of conjugates of T4, T3, and T2 in liver, and probably tissues, may make for an added contribution to thyroid hormone effect as well. Nonetheless, it is still not established that T3 is more than a by-product of the metabolism of T4 after T4 has produced its effect.

Thyroid Hormone Synthetic Cycle. These steps will be presented in broad outline only. Iodine generally enters the body with the diet as iodide, is absorbed into the blood stream whence it diffuses into the tissues, or reaches the thyroid, where it is selectively "trapped" or concentrated, or is excreted by the kidneys. As blood concentration is lowered by these latter two organs, the tissue concentration falls correspondingly. In the thyroid, iodide is oxidized to a form which reacts with, and iodinates tyrosyl residues on proteins, forming first monoiodotyrosine (MIT) and then diiodotyrosine (DIT). Two molecules of DIT are combined to form thyroxine, although the combination of one molecule of MIT and one of DIT may occur, to form triiodothyronine. Excess of thyroxine within the gland may be deiodinated, and DIT may be deiodinated, to release iodide which reenters the cycle. Thyroxine once formed may be released into the blood, or stored as thyroglobulin in the colloid, for later breakdown of the protein and discharge as T4 into the blood as needed.

Genetic Control Over Thyroid Hormone Synthesis. Strong evidence is now available that virtually every known step in the synthetic cycle may be controlled by specific enzymes, and that each of these enzymes may be derived from genic activity.[5,6] Thus, congenital goiter has been found to result from failure of iodide trapping; inability to oxidize iodide for incorporation; failure of deiodination of DIT; failure of DIT coupling; from formation and release of an abnormal thyroglobulin; and finally, possibly from formation and release of a compound having the chromatographic characteristics of T3 but not its metabolic activity.[7] However, onset of goiter in this last was not observed till age 12.

Evidence for the genetic origin of these various defects has been obtained by the demonstration of the presence of the same chemical defect in other members of the family. Such

From the Department of Medicine, Columbia University College of Physicians and Surgeons, and the Presbyterian Hospital in the City of New York.

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familial documentation is available for all of the steps in synthesis but failure of trapping, as well as for the release of abnormal thyroglobulin.[8] Since congenital goiter almost inevitably results in nodule formation within the gland, and frequently in functional failure of the gland later in the course, the possibility exists that many instances of adult non-toxic nodular goiter may result from a slowly progressive inherited defect. The evidence that there may be genetic interrelations among non-toxic goiter, toxic goiter and hypotyroidism will be discussed later.

Effect of Thyroid Hormone Upon the Nervous System. The fundamental action of thyroid hormone upon the body cell has not been defined. However, oxidative metabolism becomes decreased as does over-all cellular activity in the absence of the hormone and these effects are rectified upon hormonal replacement. With excesses of thyroxine, progressively greater effects are induced until abnormal levels of metabolic activity are achieved. The central nervous system, however, shows little if any response over normal to thyroid hormone excess as measured by oxygen and glucose consumptions,[9] though the system is markedly affected by hormonal deficiency.

Since the present discussion primarily concerns the adult, the striking effects will not be detailed of thyroid hormone deficiency upon the growth and development of the nervous system. The reader is referred to the excellent recent review of Eayrs on the subject of the thyroid-nervous system relation.[10] Essentially, the effect of experimental thyroid hormone deficiency represents a distortion rather than retardation of growth with the result that there is a considerable reduction in the probability of axodendritic interaction between neurones.[11] This amounts to the considerable factor of about 80% in the 24-day-old rat according to one method of assessment. Similarly, the extent of the vascular bed is reduced so that the cerebral tissues are served by a relatively small number of dilated capillaries.[12] Thus, more remote tissues are at a nutritional disadvantage and the capillary surface available for metabolic exchange is diminished.

Enzymatic defects in the developing brain have only recently been described consequent to hypothyroidism in the rat. A significant depression in both cholinesterase and succinic dehydrogenase activities has been reported though cytochrome oxidase and aldolase activities were unaffected.[13]

Experimental studies of the effect of replacement therapy in the cretinous rat until recently have been thought to indicate there is anatomical and functional restitution if treatment is given early enough. However, more recent studies by Bradley and co-workers[14] indicate that functional impairment can be demonstrated by more difficult behavioral tests and by EEG. Eayrs states that extent of impairment is directly related to the age at which therapy was begun. Similarly, succinic dehydrogenase activity of the cerebral cortex of the cretinoid rat returns to normal only if treatment is initiated before the tenth day of life.[13]

In the human adult, the effects of hypothyroidism have been studied at length. Decreases in blood flow, and in O_2 consumption and glucose metabolism by the central nervous system characterize the disorder, but as stated previously, thyroxine excess appears to make little detectable change from normal in these parameters.[9] On the other hand, marked irritability of the autonomic nervous system with hypersensitivity to epinephrine characterizes the hyperthyroid state.

Effect of CNS Upon the Thyroid. The dependency of the thyroid for its normal functioning upon secretion of thyrotropic hormone by the anterior pituitary has been shown to have the character of a "servo" or negative feedback mechanism. Thyrotropin (TSH) excess causes hyperfunction of the thyroid, and thyroid hormone excess depresses thyrotropin release with decreased thyroid activity. In fact, advantage has been taken of these responses for the purposes of clinical testing.[1] When thyrotropin is injected into the patient with myxedema due to primary atrophy or chronic thyroiditis, the thyroid fails to respond, but does react readily when the myxedema is secondary to pituitary failure. Conversely, thyroidal uptake of I-131 is decreased markedly in the healthy subject given thyroid or triiodothyronine for four or more days, but is decreased insignificantly in patients with hyperthyroidism. Interestingly, this abnormal response may not disappear in some patients for many years after effective treatment has been provided.

Recently, the old concept that the hypothalamus controls the release of the pituitary hormones, a concept discredited by the classic experiments with hypophysectomy, has been revived. For thyrotropin, specific areas in the hypothalamus in the median and paraventricular nuclei have been implicated.[15] Destruction of these areas in the rat results in only minimal secretion of thyrotropin even in the face of the

goitrogenic stimulation provided by anti-thyroid drugs. Stalk section in the rabbit works similarly, and injection of the hypothalamic areas with thyroxine also suppresses pituitary thyrotropin release although injection of the pituitary gland proper does the same.[16]

However, the production of hyperthyroidism by hypothalamic stimulation and consequent excessive thyrotropin release from the pituitary has been accomplished only by Harris and co-workers, in the rabbit;[17] confirmation in this and other species has so far been wanting. Attempts to find corresponding areas of control higher in the CNS have also been fruitless. Nonetheless, the common view that emotional stress leads to the outbreak of hyperthyroidism has sustained the belief that the hypothalamus may be an important link between the emotions and the thyroid..

Psychiatric Aspects of the Etiology of Toxic Diffuse Goiter (Graves' Disease). The claim has been made that over 80% if not all hyperthyroid patients were seriously disturbed emotionally at the time they became toxic.[18] Acute, unusual, emotionally traumatic episodes antedate onset in a minority of patients, whereas the presence of chronic stress is considered to be the rule. Psychodynamically oriented studies have supported the theory that hyperthyroid patients are unusually similar in some basic characteristics. A single important interpersonal relation is present in these patients which is disrupted or threatened at the time of the outbreak of hyperthyroidism; and this threat forces the patient to face his lifelong fears of separation from a protective mother figure.[19] Since not all patients subjected to this sequence develop overt hyperthyroidism, other determinants are assumed to play a role in the onset of disease.

The case for an emotional origin rests primarily upon the consistency with which emotional factors are found to precede the onset of illness and on the widespread agreement as to the developmental dynamics of the personality structure. A similar appraisal of various control groups would thus seem to have importance in substantiating these conclusions. In fact, Seldon's study has already suggested the possible importance of emotional factors in non-toxic goiter where 4% of 377 cases were found to have had acute severe emotional trauma relative to a death or injury to a member of the family prior to onset.[20]

At our instigation, Dr. Joseph M. Lubart of the Department of Psychiatry undertook a study of patients of similar age, sex and background, with non-toxic goiter coming to the Thyroid Clinic and compared these with a few patients euthyroid after successful treatment for hyperthyroidism.[21] There were nine patients with non-toxic diffuse goiter, nine more with non-toxic nodular goiter, and 14 patients successfully treated for toxic goiter, all but one being toxic diffuse. Both groups had had equally severe early emotional instability from family problems. The personality structures of the two groups were considered to be qualitatively different: toxic goiter patients were uniformly compulsive (13 of 14) and more organized in their defenses than the non-toxic group which showed only 9 of 18 with a compulsive personality, and these were considered to show less organization and more free floating anxiety. However, all of the non-toxic group as well as the toxic group had to be considered as neurotic. Unfortunately, the series is too small to be sure that it is representative, and there is no control group of healthy subjects to patients with no thyroid disease, of the same age, sex, and educational and financial background.

Nonetheless, the results obtained seem to indicate several possibilities: 1) emotional trauma may act to induce non-toxic as well as toxic goiter in the presence of appropriate other determinants; 2) the incidence of emotional factors in both toxic and non-toxic groups may be no greater than in the general population, and the relationship between the emotional symptoms and thyroid disease may be purely coincidental and not causative, or 3) the factors, genetic or other, involved in the causation of hyperthyroidism or in non-toxic nodular goiter may also have a role in forming the personality structure. Obviously, further work is indicated.

One other point of considerable importance in attempting to appraise the problem is the accuracy with which the onset of hyperthyroidism can be timed. Thus, a death of a parent or a hysterectomy followed shortly by the outbreak of overt hyperthyroidism may fit well with the concept of a threat to the patient's dependent role acting as a trigger mechanism. But some patients at least may require years for the disorder slowly to progress through euthyroidism to evident hyperthyroidism, as documented in one patient at least in our clinic.[22] Thus the frequency with which this happens must be determined before a causative role for emotional factors can be accepted.

The demonstration that the hypothalamo-pituitary axis fails to respond to administered thyroid hormone in Graves' disease, has aroused hope that the link between the emotions and the

thyroid disorder may have been found and that central nervous system activation ultimately results in sustained pituitary hypersecretion with consequent hyperthyroidism. The numerous arguments pro and con re the existence of pituitary hyperactivity in the disease have been detailed elsewhere[1] and will not be reviewed here.

Genetic Aspects of the Etiology of Graves' Disease. Strong evidence has been accumulating that there is a genetic component to the origin of hyperthyroidism. This subject has only recently been reviewed by Kitchin and Evans.[23] Roughly 20% to 35% of hyperthyroid patients seen routinely gave a family history of hyperthyroidism or of non-toxic goiter. More detailed family studies of Bartels[24] in 207 probands with Graves' disease revealed an average 60% incidence in the patients' families with a predisposition to some form of thyroid disease, as against a 33% incidence in the families of propositi with toxic nodular goiter. Bartels estimated the frequency of the gene at 12.6%, and stated the disease "is inherited in a recessive manner with partial penetrance and sex-limitation to woman, and that the gene expresses itself either as Graves' disease, non-toxic goiter, nodular goiter, or simple goiter, or perhaps myxedema." The penetrance in women was reported to be between 50 and 100 per cent.

Identical twin studies in hyperthyroidism prove to be particularly intriguing in this regard. A total of 16 pairs of identical twins are available for analysis. In the most recent study, two pairs of twins were observed.[25] In the first pair, onset was at age 44 in both, 4 months apart; in the second pair onset was at age 41, 1 month apart. Grand mal at the menarche occurred in both of the latter twins, continuing in one of the two. Proof of identity was obtained by blood grouping in the second of the two pairs. In one pair, there were five other siblings, two males and three females. Hyperthyroidism was present in one of the five, a sister. In a survey of 13 of the other 14 pairs made by Bartels, concordance for Graves' disease was noted in 10 of the 13, whereas in 33 fraternal twins, concordance was present in only four.

In toxic diffuse goiter, Martin and Fisher also found evidence of a genetic factor, but were not able to do so in toxic nodular goiter.[26] Despite this, since simple goiter, non-toxic nodular goiter and myxedema have a greater incidence in the families of patients with Graves' disease, the idea of a gene with different modes of expression has gained ground, even though the rapidly increasing incidence of nodules in the thyroid after age 40, and diagnostic difficulties in the absence of adequate laboratory data, render the validity of the evidence from the past highly uncertain.

Most recently, the presence of a common hereditary basis for thyroid disorders may have been provided by the discovery that autoimmune antibodies may be present in a number of thyroid disorders.[27] Thus, precipitating antibodies, complement fixing antibodies, and a cytotoxic substance have been demonstrated in high incidence in the sera of patients with Hashimoto's chronic thyroiditis, in primary myxedema, in hyperthyroidism, and in some normal subjects. A recent study of 39 of 44 siblings of such patients revealed that 56% of these and two of 12 distant relatives had such circulating antibodies whether thyroid disease was present or not.[28] Of the 11 siblings with thyroid disease, seven had simple goiter, two had myxedema and two had been operated on for hyperthyroidism. These data appear to satisfy the criteria of a dominantly inherited trait, since there is a 50% incidence of autoantibodies in the siblings (with half their genes in common with the propositi) and a 25% incidence in the more distant relatives (with a quarter of their genes in common).

The assumed direct inheritance of this phenomenon however is in some conflict with the recessive mode of inheritance claimed for Graves' disease. If a common gene is involved, it might, in some disorders, behave as a dominant and in others as a recessive agent. Should, however, the discrepancies be settled in favor of a single gene with varying expressions by the thyroid, so that thyroiditis, non-toxic nodular goiter and myxedema are produced as well as hyperthyroidism, the concept that a specific emotional constellation is required as the "trigger" in hyperthyroidism would be difficult to accept unless equally specific "triggers" exist for the various other disorders as well.

Effect of Thyroid Hormone on Mentation

There is little doubt that hyperthyroidism is associated with undue emotional instability and nervous irritability. Interest has been aroused recently in the extent to which the autonomic nervous system is involved in the production of these manifestations, as evidenced by hypersensitivity to epinephrine in its effects on blood pressure, blood sugar, and by the close resemblance of the manifestations of the disease to an anxiety state. As the symptoms develop, the patient's behavior may appear hypomanic. As loosening of associational trends and apparent

acceleration of thinking progress, the patient can become confused, disorientated and delusional to a degree typical of a toxic psychosis. It has been estimated in one survey that one in five patients could be considered psychotic, though not to the point of hospitalization; and in another study that 9% of hyperthyroid patients were schizophrenic.[29]

The results of an unpublished study by Dr. Chas. C. Hogan of our Department of Psychiatry is of interest in this direction. He reviewed the records of surgically treated hyperthyroid patients over a 10 year period and culled from these 70 patients who had been followed in the Thyroid Clinic for three years or more.[30] Of the latter, 70, three patients became lost to follow-up because of admission to a mental hospital. In a small control group of patients post-gastrectomy for ulcer, only one patient had a psychosis and in a post-splenectomy group none. The incidence of psychosis in the hyperthyroid group was not significantly greater than that to be expected by chance and the factor of sampling in a small series most likely accounts for the results. Nonetheless, further investigation may possibly be warranted.

Interestingly enough, the occurrence of psychiatric disorders in myxedema was noted in the last century[31] in roughly half of patients with chronic hypothyroidism. Later, the successful treatment of most patients with advanced myxedema has led to forgetfulness of this cause of psychosis in patients in whom the mental disorder has overshadowed the other manifestations of hypothyroidism. Treatment of hypothyroidism is generally considered to be highly successful in restoring normal mentation, but residual cerebral damage has been reported by Malmquist and Kincannon in one patient, psychotic before therapy.[32] However, the treatment of this patient lasted only several months before this appraisal was made, and perhaps a longer term study might have resulted in a different outcome.

When hypothyroidism is suspected, the greatest difficulty may lie in documenting the truth of this suspicion. Whether there is such an entity as "subclinical hypothyroidism," is a bone of great contention; and when treatment results in improvement in psychotic or psychoneurotic symptoms, often after six months to a year or more, the question may be rightfully raised whether spontaneous variation rather than the therapy was responsible.

A patient in our experience illustrates exceptionally well this sequence of events and the question of interpretation as to the effect of thyroid replacement therapy versus other factors.

The patient was a 38-year-old woman at the time of her initial visit for the question of hypothyroidism. The essential details in the past were a family history of a cousin with goiter and two diabetics on the maternal side; a divorce 15 years ago after six months of marriage, with a dilatation and curettage after an abortion at this time.

Following the operation, she first received thyroid therapy. The present illness thus began 15 years before her initial visit here, when thyroid was first given. The medication was taken in varying amounts until 3½ years ago. At that time she went abroad, had an episode called "acute thyroiditis" and was given thyroid again for subsequent "nodule" formation. Two years ago, she returned to the United States and was committed by her brother, a physician, for a "psychosis." She refused shock therapy, secured release by legal action and went to a sanatorium where with thyroid therapy she improved after a year and was released. She then visited a west coast university clinic where she was told she was undernourished, had residual liver damage from hepatitis six years before, and was again told to take thyroid. She had had a year of psychoanalysis.

Upon arriving in the East, she complained of inability to get going, that her brain was "skipping" and that she couldn't remember well. She was taking thyroid 0.12 gm. daily. Her mother stated the patient was drinking alcohol excessively and frequently. Her physical examination revealed a sloyenly woman, remarkably vague and wandering in her speech with disconnected mentation and slow hesitant speech. The skin was slightly dry, her pulse 84 and blood pressure 140/80. The thyroid was not remarkable. In the laboratory, the PBI was 4 mcg.%, 24 hr. I-131 uptake 1% on thyroid.

The patient was changed to triiodothyronine for two months and felt "better." An EEG was negative and a B.M.R. was —7% + 15%. However, a month later on treatment she was "paranoid" again and thought she was being followed. She stopped the triiodothyronine herself for two months and returned clinically hypothyroid.

Thyroid therapy was reinstituted, and after one year she returned, saying she felt better mentally and was peppier. She looked well, was neatly dressed and spoke and thought in remarkably better fashion than before.

Six months after this, she married. A year and a half later, she had apparently continued successfully married. She complained of some forgetfulness and of a desire for alcohol. Her nails were noted to be long and she was still enthyroid to examination. She is currently six months pregnant.

In short, there was an uncertain background of hypothyroidism and an uncertain initial re-

sult from thyroid therapy given here. Then a striking improvement mentally and physically was observed after 1½ years of treatment. She was able to marry, to control but not eliminate her desire to drink alcohol, and to carry out reasonably normal mentation though still forgetful. She became successfully pregnant at age 42. The relative roles in her recovery of her antecedent psychoanalysis, her lessened alcohol consumption, and her meeting and marrying a sympathetic male, have to be considered in interpreting the effect of the thyroid medication. However, the evidence seems to favor the latter as the major factor.

Conclusions and Summary

The effects of lack of thyroid hormone upon the early growth and development of the central nervous system and upon glucose metabolism and oxygen consumption of the system in the adult have been clearly delineated. The effects of excess of thyroid hormone are not evident by these parameters since there is no change from normal. Nonetheless, distortions of behavior and mental functioning which may meet the criteria for a toxic psychosis may accompany hyperthyroidism as well as hypothyroidism. How important hypersensitivity to epinephrine is in the behavior of hyperthyroid patients remains to be defined.

The converse problem, the role of the emotions in the development of hyperthyroidism, is also a subject for further investigation. The high incidence of emotional stress and of a definable psychodynamic constellation of development and behavior in hyperthyroid patients does suggest an etiological role, presumably in the presence of other determinants. The need is evident for similar observations in carefully selected and comparable control material; and there is a need for highly accurate timing of the onset of the disorder in relation to possible precipitating factors or chronic emotional stress.

Similarly, the role that genetic factors play in Graves' disease requires further definition from the standpoint of a genetic etiology of the thyroid disorder and the relations between this factor and the psychiatric findings in the disorder.

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Pathogenetic Interrelations in Hypertension and Coronary Artery Disease

CAROLINE BEDELL THOMAS, M.D.

Hypertension and its satellites, cerebral hemorrhage and coronary artery disease, are the chief causes of disability and death in this country today. Despite their prevalence and the vast amount of research on the subject over the past 30 years, the pathogenesis of hypertension has proved elusive. In this complex disorder, there are disturbances of homeostasis involving the blood vessels, the blood pressure regulatory mechanisms, the heart, the kidney, the adrenal glands and the central nervous system. It has been difficult to ascertain which, if any, of these disturbances comes first and is the prime mover or cause of hypertension.

A brief review of the main theories regarding etiology may be helpful. A genetic basis for hypertension has been under active consideration since 1769, when Morgagni propounded the thesis that cerebral apoplexy is basically hereditary.[1] Although both Platt and Sobye concluded that hypertension is inherited through a single dominant gene, our studies suggest multifactorial inheritance.[2-4] Pickering and others in Great Britain have emphasized the thesis that blood pressure is inherited as a graded characteristic, like height.[5,6] However, geneticists have not attempted to explain the exact mechanisms through which the genes regulate the level of blood pressure. If hypertension is truly multifactorial, a number of different enzymes may well be involved in accordance with Beadle's "one gene to one enzyme" theory.

The hypothesis that the kidneys are responsible for hypertension was first proposed by Richard Bright in 1836.[7] Almost a century later, Goldblatt and his co-workers produced hypertension experimentally in dogs by partial constriction of the renal arteries.[8] In the presence of the renal ischemia thus produced, the kidney secretes renin, a proteolytic enzyme, which acts on renin-substrate in the blood plasma to form angiotensin, a strong pressor agent.[9,10] Although increased concentrations of angiotensin have not been convincingly demonstrated in the blood of hypertensive patients, the fact that, through new techniques, unilateral obstruction to renal blood flow is detected in an increasing number of hypertensive patients and the evidence that removal of a single kidney may restore blood pressure to normal support the renal theory of hypertension.

The concept of a neurogenic origin of hypertension stems from the discovery of the blood pressure regulatory function of the carotid sinus and aortic depressor nerves by Hering in 1927.[11] When blood pressure rises, these afferent nerves carry inhibitory impulses from the stretch receptors in the artery walls to the vasoconstrictor and cardioaccelerator centers in the medulla, thereby decreasing the activity of these centers.[12,13] Chronic arterial hypertension may be produced in experimental animals by transecting all four of these moderator nerves.[14,15] In contrast to dogs with renal hypertension, dogs with such neurogenic hypertension have very unstable levels of blood pressure and heart rate.[16] In this respect, dogs with neurogenic hypertension resemble those hypertensive patients whose blood pressures are much lower when recorded at home than in the physician's office.[17] Volhard thinks that the carotid sinus and aortic blood pressure-regulating system plays a primary role in the genesis of human hypertension, with understimulation of the sinoaortic regulatory system resulting from degenerative processes in the vessel wall.[18]

A hormonal basis of hypertension is firmly established in certain rare disorders of the adrenal gland which are accompanied by elevated blood pressure: phaeochromocytoma, Cushing's syndrome and primary aldosteronism. These disturbances result from excessive or abnormal secretion of the various adrenal hormones. Proof of a causal relationship in these human "experiments of nature" lies in the return of blood pressure to normal after removal of the tumor or of hyperplastic adrenal tissue. An endocrine basis for essential hypertension is far less clear. It is known, however, that hypertensive patients have a disturbance in sodium metabolism, and recently Genest, measuring urinary aldosterone, has found evidence to suggest that human hypertension is caused by a mild, chronic hyperaldosteronism.[19]

From the Johns Hopkins University School of Medicine, Baltimore, Maryland.

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The exact role of the pituitary gland in the production of adrenal hyperactivity has been extensively studied. As part of his theory of the general adaptation syndrome, Selye has propounded the concept that stress is the basis for hypertension.[20] From his animal experiments, he concludes that nonspecific types of stress, acting by unknown pathways, stimulate the anterior hypophysis which in turn stimulates increased production of adrenal cortical hormones and that these substances affect the kidneys, with resultant intrarenal arteriosclerosis and hypertension.

While these diverse theories have been under intensive investigation in the Western World, the Russians have been strikingly consistent in regarding essential hypertension as a cardiovascular neurosis.[21] In harmony with Pavlov's general view that the cerebral cortex controls the activity of all internal organs, Soviet scientists have proclaimed the cortical origin of hypertension. In 1948, Lang was the first to present a rounded and integrated view of arterial hypertension based on Pavlov's concept.[22] He proposed that hypertension is initiated by a disturbance of the normal inhibitory effect of the cerebral cortex on the hypothalamic vasomotor centers. Their resulting increased excitability leads to exaggerated pressor responses, producing periods of transient increase in blood pressure due to vasoconstriction. This labile hypertension is ultimately superseded by stable elevation of blood pressure, with secondary renal, cardiac, cerebral and endocrine involvement becoming increasingly important in the later phases. He believes that the initial cerebral cortical disinhibition results from prolonged psychic stress, particularly suppressed "negative" emotions such as fear, anger and resentment.

While emphasis on the role of psychic trauma in the etiology of hypertension is not new, the Russians have gone much further than western scientists toward establishing this hypothesis through animal experiment. In elaborately maintained animal colonies, they have been able to develop stable hypertension in dogs and monkeys with experimental neuroses produced by conflict situations. In this country, Gantt has been a pioneer in producing elevation of blood pressure in neurotic dogs through Pavlovian conditioning.[23] Psychiatrists have emphasized the presence of suppressed resentment, hostility and rage in hypertensive patients, and such animal experiments may give support to those who consider that these and other "neurotic" traits such as subnormal assertiveness and obsessive-compulsive behavior may precede and be responsible for the appearance of hypertension.[24-29]

Thus the concept of what hypertension really is varies so much from one investigator to another that the geneticist, the pathologist, the physiologist, the endocrinologist, the neurologist and the psychiatrist bring to mind the story of the six blind men and the elephant. The first man feels the trunk, the second the leg, the third the tusk, the others the ear, the side and the tail. The first blind man says, "An elephant is like a snake." The second one cries, "No, it's like a tree." The third man protests, "You are both wrong; it's like a spear," while the others argue that it's like "a fan," "a wall," or "a rope." The problem is to bring together the many hypotheses of the etiology of hypertension in such a way that we can see the elephant.

In 1946, we embarked upon a new approach to the understanding of the pathogenesis of hypertension and of coronary artery disease, with which it is closely linked.[30] In a long-term prospective investigation of the precursors of hypertension and coronary disease, we are studying the occurrence, nature and interrelationship of certain genetic, physiological, metabolic and psychological characteristics in healthy young adults, with the Johns Hopkins medical students as subjects. We are following them over the years to determine which factors or constellations of factors are most frequently associated with the early onset of disease. It is our hypothesis that multiple factors play a determining role in the etiology of these interrelated disorders. The exact form of disease and age of onset in a given individual is thought to depend on the nature and number of factors in his own genetic inheritance in combination with the particular environmental stresses encountered as he goes through life. Our ultimate purpose is to learn to prevent these disorders.

I should like to give a kaleidoscopic view of some of our findings. In the family studies, we have studied the prevalence of hypertension and of coronary disease in two successive generations.[4] Although actually the grandparents and the parents, aunts and uncles of the medical students, we shall refer to these two generations according to their relationship to each other, namely, as *parents* and *offspring*.

Table I gives the prevalence of hypertension among the offspring of three types of mating: Type I, where both parents were hypertensive, Type II, where one parent had hypertension, and Type III, where neither parent was affected. The greatest proportion of hypertensive persons

TABLE I

COMPARATIVE PREVALENCE OF HYPERTENSION (H+) AMONG THE OFFSPRING OF THREE TYPES OF MATING

PARENTAL H+	OFFSPRING		
	N	PREVALENCE OF H+	RATIO
I. BOTH PARENTS AFFECTED	121	15.7%	2.5
II. ONE PARENT AFFECTED, ONE PARENT UNAFFECTED	440	11.6%	1.8
III. BOTH PARENTS UNAFFECTED	679	6.3%	1.0

TABLE II

COMPARATIVE PREVALENCE OF CORONARY DISEASE (C+) AMONG THE OFFSPRING OF THREE TYPES OF MATING

PARENTAL C+	OFFSPRING		
	N	PREVALENCE OF C+	RATIO
I. BOTH PARENTS AFFECTED	101	12.9%	3.8
II. ONE PARENT AFFECTED, ONE PARENT UNAFFECTED	391	5.1%	1.5
III. BOTH PARENTS UNAFFECTED	794	3.4%	1.0

was found among the offspring of two hypertensive parents and the smallest proportion among the offspring of two unaffected parents. According to whether both, one or neither of the parents had hypertension, the prevalence among the offspring was 15.7 per cent, 11.6 per cent or 6.3 per cent respectively. Thus 2.5 times as many offspring of a Type I mating had hypertension as did the offspring of a Type III mating; the rate for Type II was intermediate. This descending gradation of prevalence for the three types of mating is statistically highly significant and is consistent with the Mendelian law of segregation. While the differences observed strongly suggest that they are genetic in origin, they do not, however, provide proof of an hereditary basis for hypertension. If the differences are genetic, they suggest a multifactorial rather than either a dominant or a recessive mode of transmission. It is important to note that the great majority of the offspring of two hypertensive parents are themselves free from hypertension at a mean age of 53 years. The term "hypertension" as used here is based on clinical diagnosis by a physician rather than a single blood pressure measurement, as was used by Pickering.[4,5]

A similar pattern is found when the prevalence of coronary disease among the offspring of three types of mating based on coronary disease is studied, as shown in Table II. Again a gradation in prevalence appears: whereas 12.9 per cent of the offspring of two affected parents have coronary disease, only 3.4 per cent of the offspring of two unaffected parents have it, a threefold difference.

Obesity is a disorder often associated with hypertension and coronary disease. In the case of obesity, an even greater disparity in prevalence is found among the different groups (Table III). Eight times as many of the offspring of Type I matings are themselves obese as of Type III matings. Perhaps both genetic and environmental factors are at work here.

Although the two generation trends of hypertension, coronary disease and obesity were examined individually, they are by no means separate entities. Whether hypertension, coronary disease or obesity is taken as the index disorder, the other two are always more prevalent among affected than nonaffected groups of individuals. Hypertension and coronary disease or hypertension and obesity occur in the same individual twice as often as expected, while coronary disease and obesity are similarly although not quite as strongly associated. All three disorders appear in one person nine times as often as expected on the basis of the prevalence of single disorders.

Now, let us consider the characteristics of the medical students grouped according to their own parental history. This provides a different kind of two-generation comparison: in the one we have just seen, both the grandparents and the parents of the students were classified on the basis of medical history; here the parents of the students are so classified, while the students, in good health and entirely free from clinical hypertension and coronary disease, are classified according to their own individual traits. For today's presentation we have elected to examine

TABLE III

COMPARATIVE PREVALENCE OF OBESITY (O+) AMONG THE OFFSPRING OF THREE TYPES OF MATING

PARENTAL O+	OFFSPRING		
	N	PREVALENCE OF O+	RATIO
I. BOTH PARENTS AFFECTED	41	43.9%	8.0
II. ONE PARENT AFFECTED, ONE PARENT UNAFFECTED	302	25.5%	4.6
III. BOTH PARENTS UNAFFECTED	1358	5.5%	1.0

the characteristics of two extreme groups of students—those with two definitely affected parents and those whose parents are both free from hypertension, coronary disease, obesity and diabetes. Among 743 white male students observed in the first twelve classes studied, thirteen gave a history of hypertension in both parents, eleven had a father with coronary disease and a mother with hypertension, and three reported that both parents had coronary disease. After determining that the traits under scrutiny were similarly distributed in these three small groups, we have pooled them, forming a single group of 27 subjects both of whose parents are affected with hypertension and/or coronary disease (regardless of the presence of absence of obesity). We have also analyzed the findings among 21 subjects with two obese parents (regardless of the presence or absence of hypertension and/or coronary artery disease).

First, we shall look at some metabolic characteristics. In Table IV the height, weight and highest cholesterol level of the three groups of subjects are compared.* Their mean heights are very similar; perhaps a few more of the offspring of positive parents are very tall. Significant differences are found, however, in regard to weight and cholesterol level. The offspring of two parents with hypertension and/or coronary disease are, on the average, ten pounds heavier than subjects with negative parents, while subjects with two obese parents are 18 lbs. heavier than the negative group. Twenty-five per cent of the offspring of two obese parents weigh 200 lbs. or more, in contrast to none of the negative group. The highest cholesterol levels of the two

TABLE IV
METABOLIC CHARACTERISTICS OF SUBJECTS WITH TWO AFFECTED PARENTS COMPARED WITH SUBJECTS WITH TWO UNAFFECTED PARENTS

CHARACTERISTIC	BOTH PARENTS POSITIVE		BOTH PARENTS NEGATIVE
	H+/C+ X H+/C+ (N=27)	O+ X O+ (N=21)	H-C-O-D- X H-C-O-D- (N=55)
HEIGHT			
MEAN (in.)	71.2	71.4	71.0
73" OR OVER	29.6%	30.0%	23.6%
WEIGHT			
MEAN (lbs.)	168.3[a]	176.5[b]	158.8[a,b]
200 LBS. OR OVER	7.4%	25.0%	0.0%
CHOLESTEROL, HIGHEST			
MEAN (mg. per 100cc.)	261.0[c]	257.5[d]	228.5[c,d]
300 MG./100CC. OR OVER	16.0%	17.6%	2.3%

*Statistical analysis by Dr. Mildred A. Kendrick showed that comparisons a, b, c and in Table IV are significant, as are similar comparisons in subsequent tables.

TABLE V
PHYSIOLOGIC CHARACTERISTICS OF SUBJECTS WITH TWO AFFECTED PARENTS COMPARED WITH SUBJECTS WITH TWO UNAFFECTED PARENTS

BLOOD PRESSURE: RESTING VALUES	BOTH PARENTS POSITIVE		BOTH PARENTS NEGATIVE
	H+/C+ X H+/C+ (N=27)	O+ X O+ (N=21)	H-C-O-D- X H-C-O-D- (N=55)
SYSTOLIC PRESSURE			
MEAN (mm.Hg)	116.5[a]	112.8[b]	109.0[a,b]
130 MM. OR OVER	3.7%	5.6%	0.0%
DIASTOLIC PRESSURE			
MEAN (mm.Hg)	70.9	69.5	68.1
75 MM. OR OVER	14.8%	11.1%	11.3%
PULSE PRESSURE			
MEAN (mm.Hg)	44.7	43.0	41.7
55 MM. OR OVER	11.1%	11.1%	3.8%

groups of subjects with positive parental history are very similar, about 260 mg. per 100 cc. on the average, in contrast to a mean of 228.5 mg. per 100 cc. for the negative group. One sixth of the subjects in the two positive groups have hypercholesteremia, at least on occasion, contrasted with 2.3 per cent of the negative group. We have reported a similar positive association between hypercholesteremia in the subject and a history of coronary artery disease or hypertension in a single parent.[31]

Next, we have compared some physiological variables. The resting blood pressure levels in the three groups of subjects showed only small mean differences (Table V). However, in every instance the trend was the same: the mean systolic, diastolic and pulse pressure were higher for subjects with positive parental histories than for the negative group. Only in the case of the systolic pressure were the differences significant, however.

Our approach to the psychological aspect of the study has been frankly exploratory. Because we were uncertain which, if any, psychological factors are important in the personality structure of the prehypertensive or precoronary individual, we have made major use of projective techniques, including the Rorschach test and the Draw-A-Person test, with the hope that the psychodynamic image thus reflected would be more revealing than formalized profiles derived from psychometric tests.[29,33] We have also carried out an extensive survey concerning habits of eating, sleeping, smoking, drinking, work, exercise and recreation, reactions to situations of stress, and attitudes toward and between parents.[30,34]

It will be readily appreciated that the arrangement and interpretation of this abundant material is far more complex than the analysis of our physiological and metabolic data, which are primarily quantitative. In the psychologic realm,

qualitative and quantitative components are so closely interwoven that the problem of separating a single element from its context for analysis is a serious one. In a preliminary study, the Rorschach protocols of 25 subjects with at least one parent affected with hypertension or coronary disease appeared to show more aggression-hostility, more obsessive-compulsive trends, more feelings of inadequacy, less impulsiveness and less total affective reactivity than the protocols of 26 subjects with two unaffected parents.[29] We are currently engaged in extending this analysis.

Meanwhile, let us look at a few psychologic characteristics which can be readily counted (Table VI). When smoking habits are considered, more smokers were found among subjects with both parents affected by cardiovascular disease than among those with two negative parents. We reported a similar association between smoking habits and parental history of cardiovascular disease when subjects with a single affected parent formed the larger part of the positive group.[32,35] However, when a quantitative yardstick is used without reference to content, such as the total number of positive responses to a questionnaire concerning certain habits of nervous tension or the total number of responses to the Rorschach test, no essential differences appear between the three groups.

With the hope of obtaining the sharpest possible contrast in personality characteristics, we shall now turn to a somewhat different subject grouping. Since, as we have shown, only a minority of the offspring of affected parents have positive physiological or metabolic traits, even when both parents are affected, it seems likely that the same is true of inherited psychological patterns. If so, as yet undetermined prehypertensive or precoronary personality characteristics would be found in only a small portion of the offspring of the "positive" group and might readily be overlooked. Although not certain, it is theoretically possible that these psychologic traits occur most often in those subjects who have positive physiological or metabolic traits. In a four-way grouping described by us, subjects with a positive history of hypertension or coronary disease in at least one parent and who themselves have positive individual traits are considered to be the most highly susceptible to these disorders (Group I), while subjects with two unaffected parents and without positive traits themselves are deemed the least susceptible (Group IV).[36] Groups II and III, the intermediate groups, are discordant: in Group II parental history is negative and individual traits positive, while in Group III the reverse is true. The final comparisons today are to be made on 86 students whose Rorschach tests were all administered and scored by the same team of psychologists; 46 subjects were in Group I, the highly susceptible group, and 40 were in Group IV, with low susceptibility. Only Group IV subjects with unaffected father and mothers living at 60 or over and 55 or over respectively were included in order to approximate as closely as possible a truly negative parental history.

TABLE VI

PSYCHOLOGIC CHARACTERISTICS OF SUBJECTS WITH TWO AFFECTED PARENTS COMPARED WITH SUBJECTS WITH TWO UNAFFECTED PARENTS

CHARACTERISTIC	BOTH PARENTS POSITIVE		BOTH PARENTS NEGATIVE
	$H+/_{C+}$ X $H+/_{C+}$ (N=27)	O+ X O+ (N=21)	H-C-O-D- X H-C-O-D- (N=55)
SMOKING HABITS			
EVER A REGULAR SMOKER	68.0%	50.0%	54.0%
CIGARETTE SMOKER	44.0%	40.0%	38.0%
HABITS OF NERVOUS TENSION SURVEY			
MEAN NO. OF RESPONSES	6.8	5.4	5.9
MORE THAN 7 RESPONSES	37.5%	31.6%	40.0%
TOTAL RESPONSES TO RORSCHACH TEST (R)			
MEAN R	39.9	39.7	37.2
40 OR MORE R	45.8%	42.9%	37.3%

TABLE VII

HABITS OF NERVOUS TENSION

USUAL RESPONSES GIVEN BY SUBJECTS WITH HIGH AND LOW SUSCEPTIBILITY TO HYPERTENSION AND/OR CORONARY DISEASE (H+/C+)

RESPONSES WHEN UNDER SITUATIONS OF STRESS	SUSCEPTIBILITY TO H+/C+		TOTAL POPULATION (N=600)
	HIGH GROUP I (N=61)	LOW GROUP IV (N=47)	
GENERAL TENSION	85.2%	83.0%	80.0%
INCREASED ACTIVITY	70.5%	63.8%	67.2%
UNEASY OR ANXIOUS FEELINGS	45.9%	36.2%	44.3%
INCREASED DIFFICULTY SLEEPING	40.6%	34.0%	43.0%
LOSS OF APPETITE	36.1%	36.2%	38.7%
URINARY FREQUENCY	32.8%	29.8%	29.3%

In a survey of "habits or nervous tension," or reactions under situations of stress such as competitions, examinations or family situations, each student choses from a list of 25 types of response all the ones which are characteristic of him. The six most usual responses are given in Table VII, together with the frequency of each response among the subjects with high and low susceptibility and among the total population.[34] In none of these comparisons is Group I significantly different from Group IV, although Group I subjects give a higher percentage of responses for every item except *loss of appetite.*

When the more unusual responses are considered, however, several significant differences ap-

pear. Highly susceptible subjects more often experience *anger* and *tremulousness* under stress, and have a tendency toward an *increased urge to eat*, an *urge to confide and seek advice*, and, rarely, toward *nausea* (Table VIII). A significantly greater number of subjects with low susceptibility experience an *urge to be alone* (Table IX). They also more often tend to have an *increased urge to sleep, decreased activity* and *gripe sessions*. All in all, subjects with low susceptibility seem to be less stimulated by situations of stress than those with high susceptibility.

I hesitate to discuss our Rorschach findings since we are really only at the beginning of our Rorschach evaluation. Individual Rorschach tests have been administered, scored by the technique of Beck, and the scores transferred to IBM cards. The comparisons are based entirely on these scores. Moreover, since we have found differences in the mean scores for tests administered by different psychologists, the groups compared here are limited to those whose tests were administered and scored by the same team of psychologists.[34]

Four of the determinants in which subjects with high susceptibility to hypertension and/or coronary disease seem to differ from the group with low susceptibility are shown in Table X. About three times as many Group I as Group IV subjects gave an usually high number of popular responses, anatomy responses and pure color responses. Ego strength, as indicated by F+%, was somewhat higher for Group I. In addition to the differences shown, Group I had a higher mean number of animal responses (A) (Group I, 9.4, Group IV, 7.6). Also, twice as many Group I as Group IV subjects gave 4 or more white space responses. Group IV, with low susceptibility, on the other hand, had about twice as many subjects with superior organizational activity as indicated by high Z scores, and twice as many with a large number of fantasy responses as in Group I (Table X).

TABLE VIII

HABITS OF NERVOUS TENSION

UNUSUAL RESPONSES MORE FREQUENTLY GIVEN BY SUBJECTS WITH HIGH SUSCEPTIBILITY TO HYPERTENSION AND/OR CORONARY DISEASE

RESPONSE WHEN UNDER SITUATIONS OF STRESS	SUSCEPTIBILITY TO H+/C+		TOTAL POPULATION (N=600)
	HIGH GROUP I (N=61)	LOW GROUP IV (N=47)	
URGE TO CONFIDE AND SEEK ADVICE	39.3%	23.4%	27.7%
ANGER, EXPRESSED OR CONCEALED	32.8%[a]	14.9%[a]	22.2%
INCREASED URGE TO EAT	27.9%	14.9%	16.5%
TREMULOUSNESS	27.9%[b]	10.6%[b]	18.5%
NAUSEA	6.6%	0.0%	4.3%

TABLE IX

HABITS OF NERVOUS TENSION

UNUSUAL RESPONSES MORE FREQUENTLY GIVEN BY SUBJECTS WITH LOW SUSCEPTIBILITY TO HYPERTENSION AND/OR CORONARY DISEASE

RESPONSES WHEN UNDER SITUATIONS OF STRESS	SUSCEPTIBILITY TO H+/C+		TOTAL POPULATION (N=600)
	HIGH GROUP I (N=61)	LOW GROUP IV (N=47)	
URGE TO BE ALONE	11.4%[a]	31.9%[a]	14.5%
GRIPE SESSIONS	14.8%	23.4%	14.5%
INCREASED URGE TO SLEEP	4.9%	17.0%	10.8%
DECREASED ACTIVITY	0.0%	8.5%	5.2%

TABLE X

INDIVIDUAL RORSCHACH TEST

DETERMINANTS MORE FREQUENT AMONG SUBJECTS WITH HIGH SUSCEPTIBILITY TO HYPERTENSION AND/OR CORONARY DISEASE

RORSCHACH DETERMINANT		SUSCEPTIBILITY TO H+/C+	
		HIGH GROUP I (N=46)	LOW GROUP IV (N=40)
POPULAR RESPONSES (P)	MEAN	6.6	5.9
	10 OR MORE RESPONSES	21.8%	7.5%
EGO STRENGTH (F+%)	MEAN	78.9%	73.5%
	75% OR ABOVE	65.2%	40.0%
ANATOMY RESPONSES (AN)	MEAN	2.7	2.0
	6 OR MORE RESPONSES	17.4%	5.0%
PURE COLOR RESPONSES (C)	MEAN	0.15	0.08
	SUBJECTS GIVING C RESPONSES	15.2%	5.0%

Obviously, we are only on the threshold of understanding the meaning of our psychological findings. The suggestive differences presented as examples may or may not be substantiated when larger numbers of subjects are studied. Moreover, much work needs to be done before basic psychodynamic patterns emerge. We believe, however, that a broad psychobiological approach to the pathogenesis of hypertension and coronary artery disease is fundamental to the task of discovering appropriate preventive measures.

Summary

1. The offspring of two parents affected with hypertension and/or coronary disease are significantly different in a number of ways from the offspring of two unaffected parents. On the average, they are 10 lbs. heavier, more frequently have hypercholesteremia and have higher resting systolic pressure levels. They are more likely to be smokers.

2. The offspring of two obese parents are distinguished for their own excessive weight; 25

TABLE XI

INDIVIDUAL RORSCHACH TEST

DETERMINANTS MORE FREQUENT AMONG SUBJECTS WITH LOW SUSCEPTIBILITY TO HYPERTENSION AND/OR CORONARY DISEASE

RORSCHACH DETERMINANT		SUSCEPTIBILITY TO H+/C+	
		HIGH GROUP I (N=46)	LOW GROUP IV (N=40)
ORGANIZATIONAL ACTIVITY (Z SCORE)	MEAN	31.5	34.5
	50 OR ABOVE	8.3%	20.0%
FANTASY RESPONSES (M)	MEAN	3.6	4.0
	8 OR MORE RESPONSES	6.5%	15.0%

per cent of them weigh 200 lbs. or more. They also have higher cholesterol levels.

3. Conversely, the offspring of two parents unaffected by hypertension, coronary artery disease, obesity or diabetes were lighter, none weighing 200 lbs. or more, had lower cholesterol levels and lower systolic blood pressure. Fewer of them were smokers.

4. When subjects with at least one parent affected by hypertension and/or coronary disease and with certain positive individual metabolic and physiologic traits (Group I) are compared with subjects with two unaffected parents and negative individual traits (Group IV), the following trends were noted:

a. Subjects in Group I, when under situations of stress, react more often with anger and tremulousness. They tend to have an increased urge to eat and an urge to confide and seek advice. In the Rorschach test, a greater proportion was found to have a high number of popular responses, anatomy responses, and pure color responses and a high degree of ego strength.

b. Subjects in Group IV, on the other hand, showed a significantly greater urge to be alone when under stress and tended to have an increased urge to sleep and decreased activity. In the Rorschach test there were more individuals with a high degree of organizational activity (Z) and more with a large number of fantasy responses (M).

Conclusions

The broad implications of these studies are:

1. That the offspring of different kinds of human matings have significantly different physiological, metabolic and psychological characteristics.

2. That the differences are usually not great, even when highly contrasting groups of subjects are compared.

3. That these differences are compatible with the hypothesis of multifactorial inheritance.

4. That the ability to predict high susceptibility to hypertension and/or coronary artery disease in a given individual may well depend upon the identification and appraisal of a constellation of factors rather than upon any single characteristic.

5. That when the prehypertensive or precoronary individual can be identified with precision, the prospects for the prevention of these serious disorders will be bright.

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New Perspectives in Psychiatric Research

SHERVERT H. FRAZIER, M.D.

There has been a wide range of psychiatric comment from existentialism to genetic psychiatry. Extensive investigations on patients with thyroid conditions and those with porphyria have been reported. Certainly, all clinical psychiatrists have witnessed the supposed effects of thyroid hormone on mentation. Under stimulation of thyroid hormone, patients run the full gamut of psychiatric symptomatology. Dr. Werner's[1] observations on the effects of thyroid hormone upon the early growth and development of the central nervous system, and upon glucose metabolism and oxygen consumption of the system in the adult, have been clearly outlined. He has related the fact that patients do not show effects of excess thyroid hormone on growth and development of the central nervous system or upon glucose metabolism or oxygen consumption of the central nervous system. Yet, distortions of behavior and psychiatric syndromes exist in these patients. Thus, the need for controlled investigations of these parameters on patients under similar stresses, in persons with a particular psychodynamic constellation, is essential. Certainly, detailed psychodynamic studies of both a controlled group and a hyperthyroid group of persons with similar psychodynamic backgrounds, under specific controlled stresses, are needed. Simultaneous, carefully timed studies with psychiatric as well as physiological aspects are indicated. Continued investigations, especially in identical twin studies with all means of genetic investigation, are also indicated. These means, which are essentially incidence studies based on family genealogies, and highly technical genetic chemical studies, should be utilized.

Dr. Rowland[2] has outlined the clinical and pathological aspects as well as the treatment considerations for acute intermittent porphyria. His paper is an important source of the various theories and of the current work in the pathogenesis of porphyria. This scientific clarification of the various hypothetical approaches to this basic problem is extremely helpful, and current evidence suggests there is a block in the metabolism of the delta-amino-levulinic acids in their pathway to succinic acid and a one-carbon fragment. He indicates that current investigations may lead to an understanding of the metabolic fault in this hereditary metabolic area, and that the nature of the specific enzymatic defect is rapidly being clarified. Certainly, the relationship of the metabolic fault to the symptoms of the disease will have to be explained.

Dr. Thomas[3] has reviewed the genetic and other etiologic theories of hypertension.

This leads to the consideration of the subject, "Inborn Errors of Metabolism"—that happy phrase suggested by Sir Archibald Garrod[4] in 1908. Though some of the conditions which he felt were genetically determined as enzyme or enzyme transport system defects have subsequently been proven to be defects in renal tubular reabsorption, and though his observations were made at a time when the intermediary metabolic steps in the breakdown of certain amino acids were not known, subsequent investigation of these steps by biochemical techniques at first introduced mystery into the understanding of these metabolic errors. These have subsequently been clarified. History has been rewritten, and the basic essence of the conclusions has been proven, though by different steps than originally outlined. This is one of the quirks of science requiring us all to reevaluate such judgmental conclusions. The original thesis held that an hereditary condition, characterized by the accumulation of an abnormal metabolite, resulted from the hereditary lack of an enzyme that normally removed that metabolite. That such removal might be partial and incomplete was often held. Nevertheless, Garrod supplied a mechanism that accounted for familial distribution in highly uniform and subtle disorders. He studied cystinuria, albinism, alkaptonuria and pentosuria.[5] Because the intake of certain dietary proteins caused increased excretion of related amino acids, just as other precursors caused formation of the blocked metabolite in other errors of metabolism where degradation was blocked by enzyme deficiencies, pragmatic biochemists were led to study the intermediary steps of particular enzyme systems and amino acid metabolisms. The findings of similar defects in various members of the same family led to the study of genetic implications. Thus, an entirely new area of investigation was opened which has led to the clear understanding of the metabolic pathways of the amino acids. The finding of such inborn errors of metabolism in laboratory animals (dogs), which could be produced by genetic breeding for laboratory purposes, helped to es-

tablish this kind of insight immeasurably. The subsequent awareness of the possibilities of renal tubular transport mechanisms with enzyme-like specificity led to the findings of specific amino-acidurias. Thus, this finding was an extension of Garrod's original concept to include hereditary defects in other functional systems besides enzymes. Extensive studies of the excretion of amino acids in individual members of the same family shed light on the patterns of inheritance. This was delayed by the conceptual thinking of the times, i.e., the concept of diathesis of disease, and of separate endogenous and exogenous metabolisms.

On the strength of modern findings in man and in animals, conditions previously thought to illustrate hereditary control of enzymes of intermediary metabolism led to the inclusion of the hereditary control of specific functional substances in the body other than enzymes—the so-called enzyme-like transport systems. Garrod's concept has continuing utility in medicine and science, leading to advances in physiological genetics.

Types of steatorrhea and certain types of porphyria have been added to the list of inborn errors. This extension has involved other functional proteins, such as the discrete renal transport systems, the hemoglobins, blood cell antigens and plasma proteins, now best called hereditary molecular disease, in which the clinical aspects of the disease can be referred to the hereditary molecular defect of one species of protein.

The reader is referred to the excellent monograph by Holt and Snyderman[6] on the disturbances of amino acid metabolism in which a summary of current knowledge about anomalies of amino acid excretion is reviewed. The knowledge of the specific patterns of a number of abnormal amino acid metabolisms, caused by permanent or temporary enzyme blocks, has led to a particularly promising possibility for the identification and correction of these disorders in mental deficiency.

Some investigators have begun to consider, following the clarification and classification of these amino-acidurias, that these were related to treatment problems in psychiatry, especially those treatments utilizing specific phrenotropic drugs which have effects on specific enzyme systems in brain metabolism. In recent years, the extension of knowledge concerning biochemical defects in mentally retarded persons has added to the understanding of investigators concerning the relationship of these enzyme systems to mental illness. For instance, a familial disorder, associated with a pellagra-like rash, cerebellar ataxia, mental defect and a generalized amino-aciduria called Hartnup disease,[7] was described by Baron, Dent and their co-workers. In addition, they reported the presence of abnormal tryptophan metabolites, which suggested a specific defect in the metabolism of this amino acid. Additional evidence exists in this area in the concepts presented by J. H. Gaddum[8] and by E. M. Shaw and D. W. Woolley,[9] who speculated that serotonin levels in the brain play an important part in the development of schizophrenia. The administration of tryptophan to persons brought up the important question as to whether tryptophan metabolism is the same in schizophrenic patients as in non-schizophrenic controls. Zeller[10] concluded that there is a difference in tryptophan metabolism between schizophrenic patients and controls based on studies of the urinary excretion of xanthurenic acid and 5-hydroxyindolactic acetic acid. This is extremely pertinent in view of the involvement of monoamine oxidase and its relationship to that group of anti-depressant drugs which inhibit this enzyme. Kopin[11] and Kety were unable to confirm this work concerning the difference in 5-HIAA in schizophrenics and in normal groups. This has been related to total urine output by Kopin[12] and to vitamin B-6 availability to test subjects by Wachstein and Lobel.[13] Further investigations in this area are needed to determine the fate of xanthurenic acid and 5-HIAA during their passage through the blood to the urine because of the concentration of MAO in the kidney.

In addition to these investigations, certainly the institution of biochemical genetic studies is indicated. The concept that (1) genetic determinants of organisms are particulate in nature and occur linked together in linear fashion, with the possibility of occasional changes in linkage relationships at the time of the duplication of the genetic material, and that (2) the genetic information is carried from generation to generation by a chemical substance, deoxyribonucleic acid (DNA), on which strands of the genetic information is coded, is indicative of the sequence which constitutes the "alphabet" that spells out genetic information. Though there is no evidence that permits decision as to how DNA, the genetic substance, controls protein formation, such a concept is useful, holding that genes not only control the quantitative presence or absence of particular proteins, but they also determine the qualitative properties of the proteins which are formed. This control of protein char-

acteristics may occur by genetic control of the sequence of amino acids in the protein polypeptid linkage. It may be hypothesized that occasional errors in the duplication of the protein nucleotide code may occur at the time of gene production.[11] This concept relates to clinical psychiatric investigations in that biochemical errors or biochemical results of genetic recombinations open up a whole new area of investigation of mental illnesses.

The new findings of chromosome aberrations in certain human diseases, such as Klinefelter's syndrome,[15] mongolism,[16] and Turner's syndrome,[17] also give indication of the necessity for careful biochemical genetic investigations of specific psychiatric diseases. The advances in tissue culture techniques make possible definitive and specific genetic and biochemical-genetic studies. Studies of chromosome patterns in patients with genetic diseases, as well as in psychiatric patients, are being used more frequently. Furthermore, with the introduction of newer procedures of column chromatography, these studies make it possible to measure deficits as well as excesses of specific proteins in the blood and urine.

Recently in our laboratory, Doctors Schuller, Sterling, Tabachnick and Kallmann have utilized cellulose column chromatography to study the serum proteins in normal and schizophrenic subjects, as well as in some of the genetic psychiatric disorders.

I would make a plea for continued investigations of psychodynamic, psychologic, and psychophysiologic studies, utilizing a simultaneous technique. Certainly, each contribution forms a brick which may lead to insights and understanding that will allow the building of a wall of information which will help us eventually relate the emotional productions of mentally sick persons to the organic substrate which may either produce these primarily or may initiate them secondarily.

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Symposium on the Principles and Applications of Existential Analysis

HEIDEGGER'S ONTOLOGY AND HUMAN EXISTENCE
Michael Wyschogrod

NORM AND PATHOLOGY OF I-WORLD RELATIONS
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"NARCISSISM" IN PSYCHOANALYSIS AND THE "LOVE OF ONESELF" IN EXISTENTIAL PSYCHOTHERAPY
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Heidegger's Ontology and Human Existence

MICHAEL WYSCHOGROD, PH.D.

The direct philosophical background of existential psychoanalysis is the philosophy of Martin Heidegger. To attempt understanding Binswanger without a thorough grounding in *Sein und Zeit*, Heidegger's major work, is well-nigh impossible. The problem is compounded for the English reader, as more than 30 years after its appearance, the work has still not appeared in English. During this time, it has become possibly the most influential philosophic work on the Continent, in spite of its formidable difficulty and linguistic complexity even for the philosophically trained German reader. Acquaintance with the rationale of its argument is indispensable for the student of existential psychoanalysis.

From the outset, Heidegger makes clear that his intention is to move the problem of being into the center of his philosophy. Starting with Descartes, the tendency of philosophy has been to make the problem of knowledge primary. How can the knower be certain that the ideas in his mind refer to anything outside of themselves, that knowledge is not simply of itself but of an external reality? Descartes was able to reassure himself on this point by using the idea of God. This idea has to originate from outside the mind because, if it did not, the inferior (the finite mind) would be the cause of the superior (an infinite God), a state of affairs Descartes considered inconceivable. But if God is a reality independent of the mind and if this God is a good God, then he could not possibly deceive us to the extent of presenting us with a world which exists nowhere else but in our minds. However, this argument for the non-mental reality of the external world was not convincing to everyone. Consequently, modern philosophy was left with a problem. Materialism, on the one hand, and idealism on the other, have been the traditional solutions of this problem. Both of these dominant philosophic traditions attempt to solve the subject-object, mind-matter problem by reducing one of these substances to the other. For the materialist, mind is absorbed into the realm of matter, while for the idealist it is matter that is absorbed into the realm of mind. In spite of the tremendous intellectual effort that has gone into these reductions, the feeling has persisted that there is something illegitimate about the enterprise of reduction as such. The two poles of this dichotomy, the subjective, inner world of the observer and the external world that is the object of his observation, remain sufficiently separate so as to make the various kinds of reduction appear more a kind of intellectual slight of hand than a serious solution to the problem.

A tendency of twentieth century philosophy has been to attempt a solution of the problem by preventive measures: instead of tackling the question after it has been raised, it is attempted to prevent its arising. This is the strategy of American pragmatism, of logical positivism and of phenomenology, the tradition from which Heidegger's thought stems.

For Husserl, the founder of phenomenology, the first and most vital task of philosophy is descriptive: to analyze carefully and methodically the content of consciousness. He insisted that this task must be approached without any presuppositions or theoretical constructs that go beyond the directly experiencable. Among the presuppositions he avoids is the split between subject and object. This split, argues Husserl, is not at all observable in experience. We do not experience ourselves as being conscious and then later notice entities moving into our field of consciousness. On the contrary, being conscious involves being conscious of something (Husserl terms this the "intentionality" of consciousness). A consciousness that would not be of something would not be consciousness. The result is that Husserl finds no phenomenological grounds for a division between a conscious mind and the world of which it is conscious. If this division does not arise, there is no need to construct any elaborate epistemological mechanism to bridge the two domains. With the circumventing of the necessity of bridging the gap between the observer and the observed, the door is opened for the kind of careful examination of human experience that is phenomenology at its best. The haunting fear concerning the possible unreality of human experience is displaced by the conviction that the world as it appears to man in his most refined as well as crass experience is the only world he need care about. To seek a world "behind" this one is to leave reality. Finally, implicit in Husserl's method is the rejec-

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Author's Note: This paper constitutes a part of a chapter on Heidegger from a study of Existential Psychoanalysis to be published by Prentice-Hall in 1962.

tion of the distinction between "primary" and "secondary" qualities. Primary qualities, such as shape and location, actually inhere in objects. Secondary qualities, such as taste and color, are the reactions of an observer to an object and should therefore not, strictly speaking, be applied to the object as such. In broader terms, this results in the positing of two worlds: the public world of primary qualities and along with it a private world of secondary qualities, different for each individual and having no application beyond his private experience. The tendency has been for values, whether esthetic, ethical or religious, to be relegated to this domain of private experience where they have only "subjective" or mental reality. All of this is unacceptable to the phenomenologist for whom all qualities appear within experience irrespective of whether they concern shape, location, color or even beauty and goodness.

From this point of view, Heidegger's raising of the problem of being is made possible by the adoption of the phenomenological method which enables him to by-pass the problem of knowledge and devote attention only to its contents, the most general of which is being. Heidegger is convinced that the problem of being is the most basic branch of philosophy because every statement man utters is an attribution of being. Every statement asserts that one thing "is" something else. In so doing, it makes use of the notion of being. This applies as much to epistemological statements as to any other. Every statement about knowledge is therefore a predication of being and from this it follows that ontology precedes epistemology. The history of philosophy, according to Heidegger, is a gradual forgetting of this insight, a process that he proposes to reverse. Arrayed against him is all of modern philosophy and a good deal of ancient philosophy. Wherever the non-ontological attitude is found, man located truth in his cognition or consciousness and thereby did not permit being to reveal itself to him. This state of ontological uprootedness is the particular malady of modern man whose technological reasoning is a splendid example of the extent to which humanly constructed forms can obstruct that receptive attitude to being to which Heidegger wishes to return.

Nevertheless, Heidegger's point of departure is the being of man. He constantly affirms his goal to be being as such but it is only through the analysis of the being of man that this goal can be approached. Implicit in this is the distinction between a being (German: *Seiendes*, the sense in which we speak of an animal or a thing as a being) and being as such, which is that in virtue of which beings have being. Now, in one sense, man is a being among other beings. But in a more important sense, man is ontologically privileged because he is the being by virtue of which being as such is revealed. It is to be noted that Heidegger does not say that man is the being who thinks of the idea of being. He apparently tries to avoid any terminology that would move the discussion to the realm of consciousness and away from that of being. Mental phenomena are interpreted ontologically: if man is the being who thinks of the idea of being, then this is expressed by Heidegger in terms of man being the creature in whom being appears. Philosophic thought is therefore in the very center of ontology, not only in the sense that ontology is the heart of philosophy, but also in the more important sense that the act of philosophizing is an event of ontological significance. Ontological philosophizing is thus not merely a verbal activity which may more or less accurately reflect being. It is itself an ontological event which expresses the being of man who, by raising the problem of being, becomes the medium through which being reveals itself. From this follows Heidegger's major methodological innovation: the approach to the problem of being through the being of man. The available portions of *Sein und Zeit* are devoted to an analysis of the modes of human being and though Heidegger does not intend this analysis to be a psychological one, it is not difficult to see how such an analysis would inevitably have psychological implications.

The term Heidegger uses for human existence is *Dasein*. Literally translated, this means "being here," but it is used in German as a rough equivalent for existence. The one thesis that is perhaps the most fundamental in *Sein und Zeit* is the radical difference that is seen between the mode of being of man or *Dasein* and that of the things of the world. Heidegger refers to non-human things as the *Vorhanden* (the term literally means "that which is present," but it conveys the sense of just being there as applicable to a thing rather than a person); these are the things of the world that are there in space and to whose mode of being man is often reduced. From this point of view, man is just another object present in world-space, whose mode of being does not differ essentially from that of other objects. For Heidegger, this constitutes a thoroughly untenable position. The main difficulty with it is that it envisages a world

in which objects appear without their being parts of someone's world, that of a human observer. We do not experience a world free of human presence in which we subsequently discover man. The phenomenon that meets us from the very first is the world that is someone's—our own. Consequently, Heidegger attributes to the very nature of *Dasein* being-in-the-world. By this he means that it is not the case that first there exists *Dasein* which can be formulated independently of the world and then a world that can be formulated independently of *Dasein*. Instead, there is a unitary phenomenon which is *Dasein* in the world; neither of the two foci of this ellipse can be formulated without the other because they constitute a unity. Man's presence in the world is therefore not a metaphysical afterthought of which only anthropology and the allied "social" sciences need take notice; rather, it is the central mode of being from and through which we gain access to being as such.

The far-reaching consequence of this approach is that Heidegger insists on ascribing ontological significance to human ways of speaking. To illustrate, let us take the example of erection of a structure which requires the use of a hammer. The worker lifts one hammer and declares it "too heavy." While this may be a usual way of talking, it is rather loose. The hammer, as such, "is" not too heavy or too light. It weighs a given number of pounds and it is this weight that the hammer "is." It may be too heavy for one person, too light for another and perhaps just right for a third. These, however, are subjective judgments which do not have ontological significance; they are often classified as tertiary qualities, strictly the subjective reactions of an observer and which cannot be predicated of the object as such. It is this point of view to which Heidegger objects. By experience, he argues, hammers appear too heavy, too light or just right. Long before men had devised methods of weighing objects, with all the complex abstraction involved in such a procedure, they could tell whether given objects were too heavy or too light for a given purpose. The reason for this is that objects of the world appear in our experience in the context of some undertaking in which we happen to be engaged at a given moment and they are therefore experienced in the context of such an undertaking. If this is so, then objects actually "are" too light or too heavy—this is the mode of being of tools or utensils in the context of human activity. The judgment that a hammer weighs a certain number of pounds presupposes an encounter with the hammer that does not take place in the context of any genuine human activity, such as building, hammering, repairing, etc., but rather an attitude of detachment in which the hammer is viewed independently, not as a tool, but as an object to be weighed. Such an objectifying attitude is possible and even legitimate in certain contexts. But this is not the usual way in which we encounter the world and the objects in it. Consequently, argues Heidegger, it makes little sense to ascribe to the results of such relatively unusual measures greater ontological significance than to what is experienced in real life, in the context of real human activity. Furthermore, weighing and measuring in an "objective" way are possible only because we first encounter objects in the context of concern where they function as extensions of human being. As such, Heidegger refers to them as the *Zuhanden* (conveying the sense of being available for some human activity and functioning as a tool in such activity). We experience objects as tools long before we are able to extricate ourselves from our concerns and view them as *Vorhanden*.

We have been discussing two ways in which the world and the objects in it are encountered: in the context of activity as tools and in the context of detachment, as things. Perhaps somewhat loosely, we have referred to these as modes of being. Traditionally, philosophy has referred to modes of being as categories. Aristotle, in his *Categoriae*, classified all assertions we can make about anything into ten groups of categories: substances, quantity, quality, relation, place, time, position, state, action and affection. Aristotle seems to mean that whenever we speak of anything, we can say what it is (substance), how many it is (quantity), what its characteristics are (quality), its connection with other things (relation), etc. What categories are operating in our minds is a matter of great importance because it is this which determines what we will discover in the investigation of any problem. It is in terms of these categories that we pose our questions and which determine the answers we receive. At this point, Heidegger makes the interesting suggestion that the traditional categories of philosophy are the appropriate ways of speaking about things but not appropriate for speaking about man. As an example let us observe how the category of place applies to things and then to man. The place of all things is in space—that "in" which all things are. It is the relationship of "in-being" that must be grasped if we are to understand the

category of place. In the case of things, this works out without difficulty. A chair, for instance, is said to be in the room, the room in the building, the building in the city, the city in the country, etc. Objective "in-being" is therefore a spatial relationship in the sense described.

We also speak of man being in the world and if we carry over our categorical understanding of "in-being" without alteration, this turns out to mean that man, as a physical thing, is in the world. According to Heidegger, this would be a grave misunderstanding of the observation that man is in the world. The world, for man, is his dwelling place; he lives or resides in it. This act of living or residing somewhere is not simply a loose and humanly tainted way of expressing the fact that man's body occupies world-space. Living or residing somewhere is an original mode of human being not reducible in any way to categorical and therefore spatial "in-being." When categorical in-being is applied to man, the almost inevitable consequence is that he is divided into two parts: his body which is in space and his soul which is not. If we would avoid this duality, and not lose the concept that the being of man in the world is different from the being of a thing in a room, we must free ourselves from thinking of man in categorical terms. Such terms are appropriate to the being of things but not to that of *Dasein*. As an existentiality (Heidegger's term for that which corresponds to categories when applied to human being), "in-being" as dwelling in the world, is inherent in the nature of human being.

Categories have something external about them, they do not enter into the being of the objects to which they apply. Existentialities, for Heidegger, seem to be *a priori* constituent elements of human being. A thing is what it is more or less independently of its place while *Dasein* is inconceivable without a world in which it is. We cannot formulate *Dasein* independently of the world, subsequently to discover that it is in a world. It is part of the very being of man to be in the world as his place of residence. The world enters into the being of man unlike the way the category of place enters into the being of a thing. It is in Heidegger's discussion of time that the distinction between categories and existentialities becomes sharpest. Corresponding to categorical space, there is "vulgar" time in which non-human objects "are." This time is characterized by two major features. First, it is something "in" which all events transpire but it does not enter the being of the objects that are in time. Secondly, it is made up of an infinite number of "presents," themselves instantaneous and non-temporal, the infinite succession of which constitutes the passage of time. These two characteristics of time are related and reinforce each other. The things that are in time have their being at any given moment in a present that is not itself caught in the flux of time. These non-temporal presents, of course, are in constant motion in that they yield ever new presents. Each present is thought of as instantaneous and fixed for the instant it lasts. Heidegger refers to this as the "now" theory of time, characterizing it as the "vulgar" or "inauthentic" conception of time. A fundamental objection seems to be that it is a basically non-temporal interpretation of time. For the "now" theory, duration or temporal extension does not enter into the instant that is the "now" because the "now" is an atom of non-temporality or absolute presence. Not only is it difficult to see how genuine temporal duration can result from such a progression of "nows," but even more important is the fact that such a theory of time inevitably implies, at least to some degree, the ontological illusoriness of time. If all things have their primary being in the present and if time is excluded from the present in this curious way, then it would seem to follow that time does not really enter the being of things. Things may be in time only in a secondary way; to the extent in which they pass from one present to the other but since their primary being is not in this passage but in the present, time as duration does not really enter into the being of that which is. To this Heidegger takes exception. Being committed to an ontology that takes as its point of departure the being of man, and being impressed by the insight that human being in its most original and characteristic way is temporal, Heidegger feels compelled to develop a notion of temporality that will leave no non-temporal atoms such as the "now" of the vulgar conception of time. The key to this is human being.

Man is "in" time, reasons Heidegger, in a sense profoundly different from that in which things are in time. To be genuinely in time involves an ontological extendedness. Man is the being who, at any given moment, "is" not simply what he is at that moment but also what he has been and, more important, what he will be. In order to understand Heidegger's meaning, one must not interpret this contention in a semi-metaphorical sense. The point here is that the nature of man is determined not by means of memory of the past or anticipation of the future.

Otherwise the past and the future would be effective only to the extent to which they enter the present as memory and anticipation. The ontological effectiveness of the past and the future would thereby be conditional on losing their status as past or future and becoming present, the only dimension for the vulgar view of time. Man, contends Heidegger, is the being who at any one time exists in more than one time—there is no such thing as one time for man. Temporality is an extension for which the past and the present are constituent parts in a way to preclude any "now" that is simple and non-dimensional. To be in time in this original, non-vulgar sense constitutes a mode of being in which the temporal being literally "is" its past and its future at any given point in time (the term "point" may be misleading because it connotes an indivisible entity, exactly what Heidegger denies in his theory of time). This reasoning may seem paradoxical. Since the past is that which no longer is and the future that which is not yet, how can any being literally be that which it no longer is and which it is not yet?

Heidegger speaks of human being as "ecstatic." Literally, this term means to stand outside or beyond oneself. It is the mode of being Heidegger attributes to man. In its simplest terms, this means that included in the being of man are structures other than himself. We have come across this already in our discussion of man's being-in-the-world. There, Heidegger had made having a world part of the being of man so that the world is not something outside of man to which he establishes a relationship, but a constituent part of his being. This is not to be interpreted that the world is in man in the sense of idealist philosophy. The world is the field of human activity and as such it is other than and distinguishable from man. But to have such a field of activity is part of man's being without which he is inconceivable. We consequently have a relationship which will come up again and again in Heidegger: *Dasein's* being something which it is also not. In its most radical form, this is the temporality of human being. To be in time means that man becomes that which he already is. To the extent that the future is not something that is simply outside of the present but is part and parcel of it, man, in moving toward the future, moves toward something that he already is. This, in fact, is the basic tension of human existence. Man is constantly in a movement toward the realization of a future that is projected in the present and which precludes the present from ever being a position of rest into which the anxiety of the future does not enter. The reason for this is that the present is never a fullness of being; it is permeated completely by non-being. It is this combination of being and non-being that is temporality.

By saying this, we have come to Heidegger's basic ontological thesis in *Sein und Zeit*. Human being, he argues, is permeated everywhere by non-being and it is only by exploring the ontological effects on man of non-being that a proper understanding of man's ontological situation can be gained. An ontology of being that has no place for non-being, such as that of Parmenides, cannot grant ultimate reality to time; in one way or another it must relegate time to the domain of illusion. Essentially, the reason for this is that temporality involves the dimension of the "not yet," of a state of being that has not yet been achieved but toward which the present is oriented. As such, that which is temporal "is not" as much as it "is": it is what it is in the present but it is not what it will become. Being in time involves a perpetual state of incompleteness that is not something accidental to man's being, but an essential part of his being. Ontologically, Heidegger feels that the radical and essential incompleteness involved in temporal being, is most adequately interpreted in terms of an ontology in which non-being is as active as being. It is true that, as Parmenides had so convincingly argued, to think about non-being involves the philosopher in embarrassing verbal difficulties which has led most philosophers to avoid thinking about non-being. However, this attitude is no longer possible because the modern situation does not permit it. We will see very soon how Heidegger draws on the dominant psychological and spiritual tone of modern man in his analysis. An ontology lacking a serious concern with non-being is inappropriate to modern man, which should have been obvious from the fruit of the Parmenidian ontology: the denial of motion. Motion, implies Parmenides, is a rational impossibility because it presumes that a thing may be at two places at the same time, something that is manifestly impossible. If a thing at any one time is only in one place, when does it move from that place to the next? It is clear that this analysis is based on a "now" theory of time which encounters difficulty in formulating a genuinely durational time in which motion becomes a possibility. From this point of view, it becomes understandable that an ontology of non-being should come into prominence at a time in history when motion and change are perhaps

the dominant characteristics of the period.

In more concrete terms, Heidegger's ontology of non-being expresses itself in his interpretation of human being as a being ahead of itself. He uses the term "Care" (Sorge) to sum up this dimension of human existence. Though he insists that this term is to be understood in a technical, ontological sense, the very choice of the term indicates that Heidegger finds certain experiences ontologically privileged in that through them man gains insight into his "being" in some special sense. To care, or to be concerned, involves several aspects of the situation in which man finds himself. It involves human temporality because being concerned about something is basically an encounter with some threat in the future and therefore with the threat of time itself. Care is also possible only for a being who lacks something or is in fear of losing something he possesses, which Heidegger interprets as encounters with non-being. It is also important to realize that care is not a relatively temporary mood which seizes us sometimes, only to release us for another mood. Care is the basic structure of human being because it is behind all human activity. Only because men care about something have they built civilizations that try to satisfy those concerns and celebrate in the form of myth and religion those concerns, which, because they cannot easily be fulfilled, are even more pressing than those that can. Care is therefore the most basic expression of human incompleteness which, in ontological terms is to be understood as the penetration and permeation of non-being into being.

It is in the existentialistic interpretation of death that the interpenetration of non-being with being is most sharply expressed. Categorically, death is the end of human life in very much the same way that the dropping of the curtain is the end of the play or the last page is the end of the book. This is how most people view the death of others: they realize that at the end of life there is death and, in the case of others, we are able to observe this cessation. Thus, irrespective of any view about afterlife, the objective or categorical view of death sees life as surrounded by a form of non-being before birth and after death. Between birth and death, however, there is life which interacts with non-being at two points only: birth and death; everywhere else it is pure being. The crucial difference appears when I consider my own death. I cannot view my death as the cessation of life in the same objective spirit in which I view the cessation of a performance for the simple reason that I cannot view it from a distance. I cannot consider my death as the cessation of my life because such a view presupposes an ability to view this process from the ouside. But I will no longer be when the cessation takes place. It follows that my own death has reality only to the extent that it functions in my life. Man is the being whose death is not the cessation of his life, remaining at the end and therefore outside of life. He is the being whose life is lived "toward" death, by which Heidegger means that death interpenetrates life at every point, making it a possibility of life in the profoundest sense. This is not to be interpreted as a fearful and paralyzing preoccupation with death. In fact, the greater the morbid fear of death, the greater are the chances that the individual in question does not conceive it in existentialistic terms. Such morbid fear results from viewing death as something outside of life which, however, threatens to enter or interrupt life and is therefore feared. It is the unfamiliar and unknown that is feared; because death is so deeply part of life for Heidegger, it cannot possibly be an object of fear. Instead, the existentialistic encounter with one's own death frees man from the fear of death by making it not a foreign body but part of the being of life from the very beginning. While Heidegger's notion of an authentic attitude toward death excludes morbid and fearful preoccupation with it, it also excludes the kind of logical gambit engaged in by the ancients when they said that death was nothing to worry about because when it is, I am not, and when I am, it is not. Ludwig Wittgenstein, in our day, seems to mean this when he writes: "Death is not an event of life. Death is not lived through." This too, from Heidegger's point of view, is an inauthentic attitude to death because by locating death outside of life, it pretends that death does not enter life and is not operative within it. Though death is non-being, it is also something very much active in human life. To express this activity of non-being, Heidegger uses the term "nichten" which is best translated as nihilating. Paradoxical as it may sound, non-being does act in human life and this activity is a negating or destroying one, threatening the foundations of human being. Human being is therefore this very involvement with non-being as the genuine possibility of human life.

The authentic encounter with the possibility of one's own death, by transforming human being into possibility, in turn makes possible a number of other existentialities. One of the most important of these is the achievement of the

status of an individual. In the inauthentic mode of being, man lives impersonally. His authority is whether "it is done." In German, this is expressed as "Man tut dass nicht." Heidegger seizes on the word "Man" to describe the total mode of impersonal being that characterizes the man of the masses. His domain is that of "Gerede" ("idle talk, prating), a mode of speech that has lost contact with the object of discourse and is therefore simply chatter (small talk in American), the main purpose of which is "killing" time. Intimately connected with this is the phenomenon of idle curiosity (Neugier). This is the realm of the popular press which specializes in the cultivation of a "peeping Tom" mentality. Here man escapes from his own concerns and substitutes for them a pseudo-concern with events which are conceived of as a form of diversion or entertainment but whose primary function is to serve as an escape from real concerns. All these mechanisms are interpreted as escapes from the solitude of individuality into the togetherness of mass-existence. There is one human possibility which cannot be encountered in the mass: death. In death, I am inescapably alone because when I encounter death as my own death, I realize that here no one can substitute for me, nor can it be a group experience. For these reasons, the individual's own death is banished from consciousness in inauthentic existence, thereby permitting the individual to live as if he were not an individual but part of a mass. This is also the reason for the fear of being alone. For authentic man death is not a far-distant threat but an ever present dimension of life; individuality and aloneness are therefore not objects of fear but the very conditions of a truly humane existence.

The achievement of individual existence is thus seen to be a direct function of an authentic understanding of death, which is the supremely individualizing dimension of human life. Such an understanding of death also liberates men from the paralyzing fear of it. To understand the import of this liberation from fear, it is helpful to make reference to the distinction Heidegger draws between fear (Furcht) and dread (Angst). The former is characterized by having a specific object. It is fear of illness, loss of a beloved one, unemployment, etc. Depending on circumstances, sometimes such fears are realistic and sometimes not, but whichever the case may be, fear has a definite object that is more or less consciously formulated by the individual. In contrast with this stands dread or anxiety. It is much less specific, it has no definitely recognizable object and it is therefore much more difficult to deal with. To experience it is to experience a diffuse foreboding, a sense of floating over an abyss. When the person at any moment is asked what is bothering his, Heidegger tells us, his answer is: "It's nothing." This answer reveals more than would be apparent at first sight. It is true that anxiety has no object; but only in the sense that its object is nothing. Anxiety is the experience of being projected into non-being or nothingness. It is the experience we have when we feel ourselves torn out of our security in being and encompassed by that which we are not. Anxiety is not an "emotion" that man may or may not have: it is the most profound experience of being human that is always present explicitly or implicitly, irrespective of the presence or absence of any specific threat. Indeed, it is the presence of anxiety that makes possible the experience of fear. Specific threats can arise only because man is a project who is threatened by non-being—the most profound threat of all.

Norm and Pathology of I-World Relations

ERWIN W. STRAUS, M.D.*

I.

Heidegger's *Being and Time* made its entrance into the world of letters in an austere academic environment. The first edition was not a book in its own right. It was published in 1927 as an essay in Husserl's "Yearbook of Phenomenology," a philosophical journal written by a professional for professionals. Yet, this newborn stood out from the other "brain children," because of its style, its scope, its themes, its depth, its approach. The starting point was a consideration of man in everyday life; the goal was to reach an understanding of the meaning of Being; and the road leading from that start to this goal were the *Analytic of Dasein.* It is therefore not surprising that the author, the title, and even the book itself were in a short time enthusiastically accepted by many and rejected with no less passion by others.

Like so many readers, psychiatrists were fascinated by the *Analytic of Dasein,* revealing the basic structure of "existence" as Being-in-the-World and Being-with, dealing with such topics as authenticity and unauthenticity, thrownness and project, dread and care, call of conscience and resolve, finiteness and temporality.

The Swiss psychiatrist Ludwig Binswanger became convinced that with *Being and Time* the philosophical foundation of psychiatry had finally been established. He tried to apply Heidegger's philosophy of existence to psychiatry, to translate the *Analytic of Dasein* into Daseinsanalysen (existential analyses). Yet on his way back and down from the ontological level to the ontic sphere he had appalling obstacles to overcome. Care, thrownness and project in Heidegger's work, just as bad faith, freedom, choice in Sartre's philosophy, are ontological concepts. How can these existentials be applied to the lives of individuals, to their actions and motions? The crucial point is the exalted position which Heidegger assigns to man. "Concerned about his Being and behaving toward his Being as toward his own possibilities," man appears to him different from all other beings—not only from inanimate things and man-made machines but also radically different from all other living creatures. For this reason Heidegger rejects the traditional definition of man as an *animal rationale.* He acknowledges, of course, our kinship with the animals, yet he emphasizes that man in his existence is separated from them by a very abyss.[1] One cannot ask, according to Heidegger, *what* man is, still less answer this question. One can only ask for the *who* and the *how.* There is no unchangeable order of natural qualities characteristic for the species, no essence in the traditional meaning of the term, which ultimately characterizes man. Therefore, Binswanger adds, one cannot make man the object of research. We understand the other only as a partner in an I-thou relation.

These theorems lead to serious consequences when applied to psychiatry. If it makes no sense to ask what man is, we no longer see him as a living creature in health and disease. Heidegger was familiar with these and other facts of life; the problem is whether and how he or his followers can incorporate such themes as physical existence, sexuality, animal nature, or disease into his ontological system. Actually Binswanger leaves no doubt that his *Daseins-Analysen* are by no means a specifically psychiatric method. That he used it primarily for the interpretation of schizophrenic cases is a kind of professional accident. Binswanger's existential analyses of Ellen West, Lola Voss, etc., move between the poles of authenticity and unauthenticity, of floundered and accomplished forms of existence—but not between normal and abnormal, healthy and sick. "Existential analysis," Binswanger wrote in 1945, "is not a psychopathology, nor is it clinical research nor any kind of objectifying research. Its results have first to be recast by psychopathology into forms that are peculiar to it, such as that of a psychic organism, or even of a psychic apparatus, in order to be projected onto the physical organism."[2,3]

However this may be, I shall make clinical experience my point of departure. In turning my attention to a typical case I do not regard him as an apparatus but as an experiencing creature. Here I believe I am entitled to claim Heidegger, if not as my master, at least as an ally, for two reasons:

First we encounter the mental patient as a stranger in our everyday-life world (the Lebenswelt, in Husserl's terminology). Whatever theories we may offer to explain psychotic behavior, whether we accept the thesis that mental diseases are brain diseases or search for a conflict between ego and id, ego and reality, ego and super-

*Director, Research and Education, Veterans Administration Hospital, Lexington, Kentucky.

ego, the frame of reference from which we start and to which we return is the structure of the everyday-life world. When Freud speaks about a break with reality, he refers to the reality familiar and common to all of us—the reality of so-called naive realism. This is the same for the learned and the illiterate, for the rich and the poor, for Lumumba and Hammerskjold. Its characteristics are not taught in school. We live it, enact it, respond to it, but we do not know it. Indeed, the failure of the mental patient to conform may cause us to stop and think about the *Lebenswelt*. Psychoses are, so to speak, basic experiments arranged by nature; the clinical wards are the natural laboratories where we begin to wonder about the structure of the Lebenswelt. We realize that in order to account for its breakdown we have to study its norm first. We suddenly notice that we are beginners in the field where we deemed ourselves masters.

Another obstacle exists. The discovery or rediscovery of the Lebenswelt has been blocked by a scientific tradition, reaching back into antiquity. The Lebenswelt was held in contempt, despised as illusory. Modern science has been even more radical in its censure and its demands. The world as it appears to us in its macroscopic structure and with its sensory qualities must be reduced to atomic events. This reduction supposedly leads from a mere appearance, in the sense of an apparition, to the real core of things. The scientific credo professes as an article of common faith, Lashley said,[4] that "all phenomena of behavior and of mind are ultimately describable in the concepts of the mathematical and physical sciences." The paradoxical consequence is that the science of physics must be understood as groups of physical events. Most psychologists, therefore, refuse to waste time in contemplating physics as a human accomplishment which originates in the Lebenswelt. They take the possibility of observing for granted. Satisfied with measurements, they do not inquire into the psychological conditions of measuring. The tables are turned; the physicist himself, or man—in all his activities—is considered as an object of physics, a body among other bodies. Human experience and conduct must forcibly be adapted to the ruling system of physicalistic concepts. But this theoretical bias obscures the very sight of the phenomena. Inadvertently and unintentionally, they are assimilated to the "underlying neural mechanisms." The dogma has it that sensations, perceptions, thoughts, memories, occur *within* a particular organism, accompanying excitations of the nervous system. They are side effects; sparkles flashing with the turn of synaptic switches which transmit afferent impulses to the motorium. Experience, and sensory experience, is supposed to be merely "subjective."

Since the days of Galileo subjectivity has been interpreted in spatial terms. Sensory qualities do not reside—to use Galileo's terminology—in things themselves; they reside in our minds; today we let them reside in our brains. From their supposedly original position percepts are carried outward—through reality testing, projection, or some other voodoo procedure—and finally located in an external world to which none of us has any direct access. Scientific theory based on Galileo's, Descartes', Hobbes' metaphysics teaches a radical sejunction of subject and object. The experiencing creature is cut off from the world.

In the practice of life, however, we do not place others in an outside world; we meet them on common ground. Obviously the reduction cannot be unilateral. One cannot reduce qualities to cortical stimulation and then talk about our brain. If the sensory qualities are relative to man, man is relative to them. The reduction does not actually change the appearance of things; it is performed in thoughts and words. The physicist never leaves the shores of the Lebenswelt. In fact, the reduction of the Lebenswelt silently presupposes its validity. We are *in* the world, not outside. There we are in contact with all things in sight and in reach. The senses do not provide us with mere sensory data. In seeing, we are confronted with the objects themselves, not with their pictorial representations. The act of seeing demands our presence; it commits us to a definite position in relation to our environment. In sensory experience we are aware of things *and* ourselves; not one before the other, not one without the other. This is the second point where I am at least in partial agreement with Heidegger, who in the *Analytic of Dasein* refutes the traditional subject—object dichotomy. I have avoided his telling term "being-in-the-world," because in *Being and Time* it is understood as an ontological concept. It signifies that mode of Being which makes the ontic structure of human life possible and understandable. For this reason the existential Being-in-the-world is limited to Dasein and cannot be applied to sensory experience in general, i.e., not to animal experience. But medical anthropology cannot omit life and the animal nature of man, although man can and usually does detach himself from the primary modes of contact, which he has in common with the animals.

All scientific observation begins on the level of sensory experience, but not all sensory experience ends on that level. Those who run for safety in a hurricane do not measure its velocity. Science demands a detached observer who projects events upon an impersonal frame of reference, which can always be identified and reconstructed. In science, observers are exchangeable; they all sit in the audience and watch the events on the stage. In primary sensory experience, however, there is no division of space into stage and auditorium; everyone is in the arena. In sensory experience we are not neutral observers watching the outcome of remote events through a one-way mirror; we are affected, caught, seized, in an egocentric position. The light, the wind, heat and cold, sounds and scents, are obtrusive; we "realize" their impact. Things appear attractive or repulsive. We respond to their physiognomies rather than to their logical order. That we are beset is decisive; the *How* and *What* is secondary. The *That* of being engaged and seized precedes the *What*. The scientific observer explores and judges the reality of events. To him the predicate "real" signifies that something has occurred in accordance with the established laws of nature. In sensory experience, however, "reality" has quite a different meaning; it means that something happens to me. Reality of sensory experience concerns me in my unique vital existence. It is before reflection and doubt, as so clearly demonstrated by the apodictic powers of hallucinations.

In some of my writings I have tried to reopen the case of sensory experience, to reclaim a territory lost for a long time. In using the term aesthesiology I have even made an attempt to reinstitute the forgotten meaning of *aisthesis*. In this I may appear quixotic, because I am compelled to challenge generally accepted doctrines of neurophysiology, such as "Mind can only be regarded, for scientific purposes, as the activity of the brain."[5] To this statement Hebb adds, "Modern psychology takes completely for granted that behavior and neural functions are perfectly correlated, that one is completely caused by the other."[6] In line with this postulate, perceptions must be considered as perfectly correlated with and caused by afferent conduction and cortical excitation. Indeed, the physiological problem of thought, Hebb explains, "is that of the transmission of excitation from sensory to motor cortex."[7] If this is so, sensory experience cannot add anything essential to the function of the body machine. But these speculations of a tough-minded empiricist leave us completely at a loss as to how he could account for his knowledge of the activities of the brain. For in every neurophysiological experiment two brains are involved: the brain observed and the observer brain. When someone studies the brain of a man or an animal, his own brain is excited by optical stimuli reflected from the surface of some remote object. The stimuli, upon their arrival upon the retina, will not tell whence they came. The so-called observations must be considered as activities which are located exclusively within the observer's brain and skull, a mere transmission of excitation from sensory to motor cortex. Not even the magic of projection could transform such intracerebral excitations into an object of observation.

Through sensory experience a new dimension is opened to the experiencing organism. This is the basic fact upon which all science rests, even the denial of the fact itself. In sensory experience we are related to objects qua objects, to an environment in which we can orient ourselves and act. The intentional relation to the other enables us to finally comprehend the order and relation of one object to another one in the physical world. The relation of a nervous system to stimuli is not commensurate with that of an experiencing being to objects. The work of neurophysiology and psychology is contaminated through the promiscuous usage of the terms stimulus and object, a confusion unpardonably confounded.

II.

The next step is to apply aesthesiology to pathological manifestations. I select a well defined organic disturbance: a mild but characteristic failure in spatial orientation. I have in mind those patients who prove unable to draw the floor plan of a room or a house, with which they are familiar and in which they still move around at ease. As Henry Head noted, aphasic patients, otherwise inconspicuous in their spatial orientation, are frequently incapable of performing this apparently simple task. Such disturbances are counted among neurological symptoms; they are considered as an impairment of a more or less isolated function, related to a focal derangement of the brain, a deficiency remote from the center of Dasein. However, I intend to show that accomplishment and failure in such cases are much more involved than assumed.

The observation of failures makes us wonder about the normal performance. The situation is typical; it illustrates the psychiatrist's embarrassment mentioned in the beginning. In everyday life we take it for granted that a nor-

mal person will be able to draw, after a fashion, the floor plan of a familiar room. Psychiatric experience puts an end to such naive confidence. We discover a problem where we had seen none before. Obviously, an explanation of this disturbance has to wait for an adequate understanding of the norm.

In the procedure characteristic for experiments we watch a transformation produced under controlled conditions. A change occurs; the initial situation vanishes with the progress of the experiment. At the end, let us say, of a chemotherapeutic study, we pause and ask ourselves whether the patients might not have recovered spontaneously, without any medication. Yet we cannot reverse the experiment; we cannot return to its beginning. The experimental code therefore requires controls. In order to provide for controls we pair, in unwarranted optimism, treated and untreated patients. In our present investigation we need no controls. We can directly match final and initial situations; both can be viewed simultaneously. The finished product will tell us more about its producer and his production than any introspective or objective methods of observation could reveal.

A floor plan of this auditorium somehow depicts this hall, although it would be difficult to discover any resemblance between the two. No likeness connects the representation with the original. The plan is not a portrait, not a facsimile; neither is it a sign or symbol; it represents but does not reproduce. In fact, comparing the representation with its prototype, one is struck by the obvious disparities, the enormous reduction of volume, size, and substance. In contrast to the fullness of the original view the outline drawn on a floor plan appears pitifully meager. In spite of its obvious inferiority the plan must in some way be superior to the original. Graphic representation, like other symbols, cannot be a mere substitute for reality. The deficiencies are obvious. It will take more effort to uncover the virtues. Perhaps we must change our point of view and search for the shortcomings encountered in the actual situation. Is there nothing wanting? At this moment we enjoy a spacious room. But let us lower the ceiling and bring the walls close together; soon we reach a point where we will feel shut in. Walls look grim to a prisoner in solitary confinement; they block his sight and action. A house in flame no longer shelters; it threatens to engulf its occupants. These are extreme situations, but they make us see, like through a magnifying glass, traits which, although inherent in every sensory experience, most of the time pass unnoticed. All walls are enclosures. Every visible thing is an object in the literal sense of the word; an objectum—i.e., something thrown against, in German a *gegenstand*—something which stands against, resists and limits our view like the tall man in the theatre who always sits in front of us. Reality holds us in the confines of the here and now. In every concrete situation the walls form barriers which our sight cannot penetrate. The floor plan, however, presents their outline as figures on a ground, as a demarcation in a space extended beyond the physical boundaries.

An architect's design shows spatial relations of rooms, such as no mortal eye has ever seen. The rooms have lost their solidity. In reality, walls separate one room from the next one; they hold us back in sight and motion. On a plan, all the neighboring rooms are open to simultaneous inspection. We recognize the walls but we see them as partitions; we see them, so to speak, from both sides at once. The architectural design presents the single room as part of a whole which, as such, is out of reach. Under natural conditions we can pass only from one part to another part; we must leave one room to enter the next one. On a floor plan we transcend without effort the natural barriers of sight, location, distance.

Blueprints and road maps are elaborate designs. But the discrepancy between the original and its representation is no less acute in the modest assignment given to our patients. The floor plan of a single room presents all four walls at once and shows inner and outer space simultaneously, a view unparalleled in reality. In the actual situation we have to turn around, replacing in temporal sequence the sight of the front with that of the rear. Yet the plan presents the whole and presents it at rest. True, it simplifies reality, but it also adds to it; it shows more than the actually visible. If abstraction means nothing but omission of details, the floor plan cannot be the result of abstraction. On a ground plan the ceiling, of course, is omitted. One may even doubt whether the white space circumscribed by the pencil lines actually represents the floor; for we may indicate the position of windows or other structures which either do not reach to the floor or rise above it. In any case, the plan represents the floor of a room; it does not simply imitate the track of lines where walls and floor meet. The plan does not give a mutilated torso of reality; height has not been amputated. Three-dimensional extension is represented on a two-dimensional plane. The actual situation is dras-

tically changed; it is radically transformed. Whoever draws a floor plan must be able to emancipate himself from the impact of reality. A change in his I-world relations is required.

The plan presents the original as it never will be seen. The spatial configuration of the room is represented not as seen from inside but as it happens to exist *per se*, visualized from nowhere, detached from the personal presence of any spectator. While paintings—at least from Giotto to Monet—pictured the world as seen by man from a concrete "point of view," the floor plan excludes its own maker. It does not show a perspective organization of space converging to a center. Reflecting upon myself, I can mark my position on the plan, inserting myself like another object into the detached order of things. On the plan I am no longer at the center of my environment. Space is not organized around me in zones of closeness and distance; space has no depth. The direction backward is eliminated and replaced by the dimension side by side. A plan does not present an abstraction from concrete sight; it translates visible space into the abstract homogeneous, isometric, impersonal order of geometry. The categorical attitude required in the construction of a floor plan calls for a reflexive dislocation of one's own self.

On a floor plan natural size is discarded. I can draw this room on a small sheet of paper; its natural size is of no consequence. The proportion (in Latin: ratio, in Greek: logos) of lengths and angles alone is important. Together with natural size, weight, location and orientation are abandoned. The plan is weightless, not because paper is light; the flimsiest sheet of paper will do, because the design is insubstantial. It could be drawn upon any other material. The material used does not "matter." In fact, it must be negligible, because a representation is not that what it materially is. It points to something else which it is not. The wall represented on a floor plan consists of bricks, mortar, paint; but a plan does not consist of paper and ink. A painting, though *on* the surface, is not seen *as* the surface of the canvas on which it is painted; it has no physical depth. Like a painting, the plan is a weightless, immaterial representation of something which it is not. Although we cannot dispense with some material, the representation as such is im-material. Were it not so, it could not function as a representation. Therefore, also, its own orientation in space is irrelevant. We can place it in any position, lift it from a horizontal to a vertical plane, turn it from north to south. All such variation do not count, because the plan does not belong to the continuum of physical space; neither has it a unique position in public time. We can draw the plan of a building in direct sight, preserve the plan of a demolished structure, or devise a plan for a building to be erected in the future. A plan serves planning. The representation, the ground plan, just as other symbols, permits a freedom of action and comprehension which excels our direct contact with the original.

Even though the final result, the plan, runs counter to the sensory experience, the initial situation must allow, even provide, for this metamorphosis. Indeed, our comparison of the original and its representation contains in itself the solution of the problem which it poses.

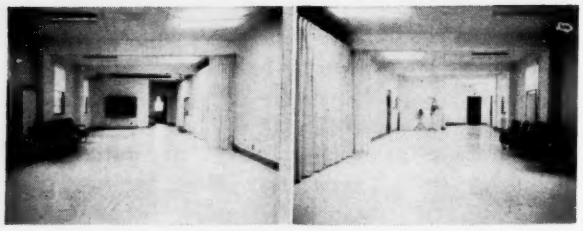
To lay it bare we will have to part with the cherished idea that a sequence of stimuli is accompanied by a corresponding series of percepts and that this multitude of single perceptions, although originally separated by each other, like individual frames in a motion picture film, could, nevertheless, be somehow joined together.

Actually, there is no problem it may be argued. We can draw a room as a whole, because, in turning around, we add the view of the rear to the preceding one of the front. It is as simple as that. Only a fool could miss this straightforward answer to our query. As plausible as such an explanation may sound, it is a classic example of a *petitio principii*: it presupposes what it tries to explain.

Every motion which has the character of "turning around" is, from the start, related to a firmly established whole as its frame of reference. Of course, if in a particular case we want to learn the conditions of a whole room, we would move and turn around. But those who offer the motion of turning around as a causal-genetic explanation for the apprehension of the whole as such, make quite different claims. They believe that this movement produces a kind of fusion between two discrete bits of excitation. Notwithstanding their disseverance, they fit together in the same way that two photos, reproducing opposite segments of a room, might be joined together. The motion of turning around supposedly permits two cortical configurations, although produced by disparate groups of stimuli, to form one figure. If allowed to meet, the fragments cling to one another like two magnetic semicircles growing together into one iron ring. In this process of optical fusion the motion of turning the body is only instrumental. It simply furnishes the occasion; the marriage broker does not share the nuptial bed. Nevertheless, be-

cause experience, as we have been told, is perfectly correlated with neural functions, our comprehension of a room as a whole is caused by the amalgamation of the two optical excitations, and indirectly by the motion which allows their junction. The genetic theory therefore demands psychophysical harmony and strict correspondence.

We may test this hypothesis by means of a fictitious experiment. We place a human subject on a small, rapidly rotating turntable in the center of a room. A light is turned off with every revolution of the table. The subject is brought into a position in which his optical receivers are hit by stimuli reflected from one part of the room (Fig. 1). After a turn of 180 degrees, his retinae will receive stimuli from the opposite sector of the room (Fig. 2). In the subject's optical system two volleys of stimuli will succeed each other (Figs. 3, 4). However, the two excitations, although following each other in objective time, cannot realize their sequence. They remain isolated. But even if they could somehow be associated, the optical system cannot provide for the supposed junction of the two halves, because it is uni-directional. The polar



Figures 1 and 2.

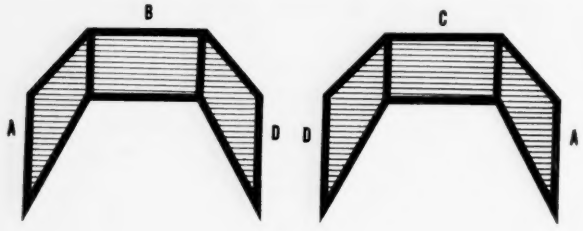


Figure 3.

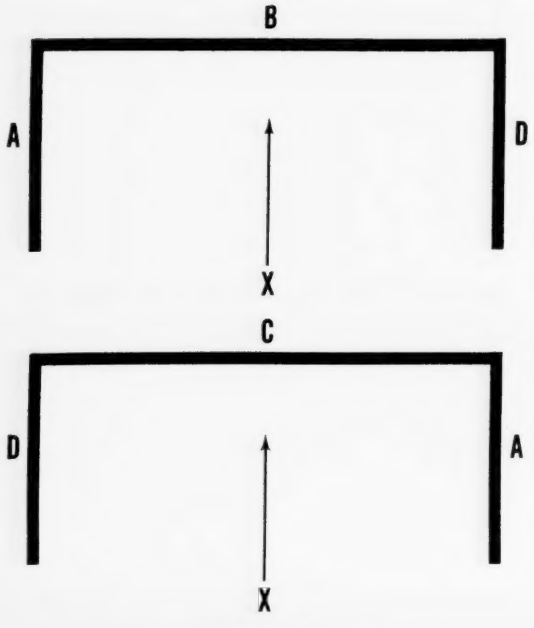


Figure 4.

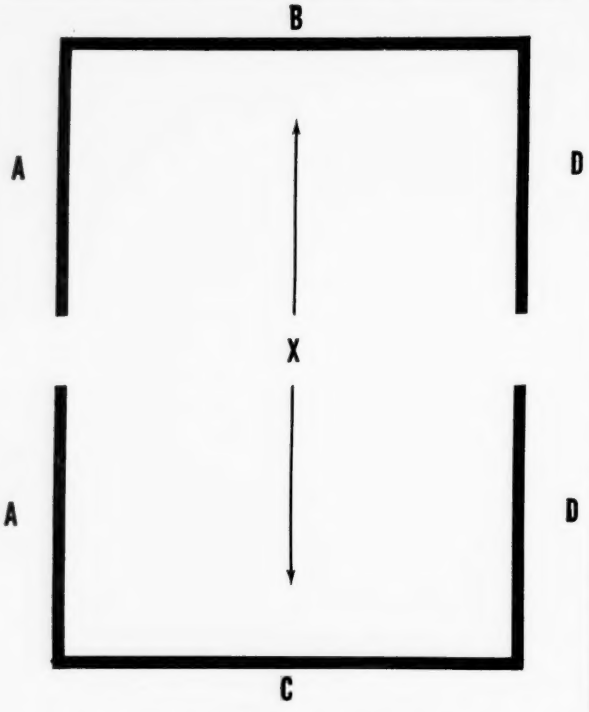


Figure 5.

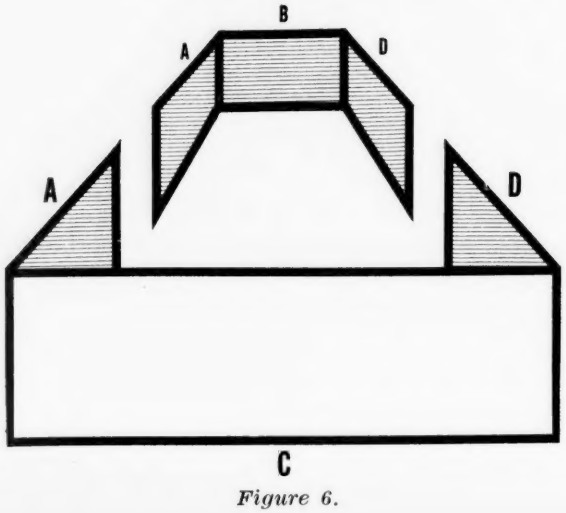


Figure 6.

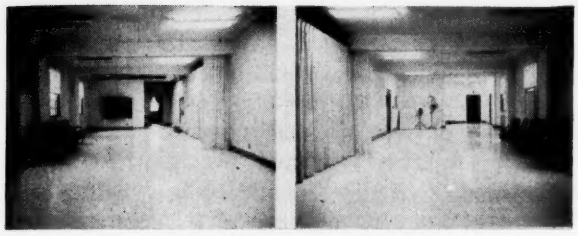


Figure 7.

Figure 8.

articulation *forward-backward* (Figs. 5, 6) is alien to it. Throughout our lives light enters our eyes in the single direction of pupil to retina; likewise, the direction of the afferent impulses and the spatial orientation of the cortical areas never change. In relation to optical stimuli, the polarity *rostral-caudal* does not apply. While we must rotate to expose our optical receivers to light traveling in opposite directions, such change is not recorded by the optical system itself. In our subject's initial position (Fig. 1), the wall B (Fig. 3, 4) was vis-a-vis to his eyes. With a turn (Fig. 2), the opposite wall C (Figs. 3, 4) is brought into obverse position to his eyes while the lateral walls A and D, to the right and left, exchange places (Figs. 7, 8). The two optical projections correlated with the positions of our subject do not complete each other as complementary halves. Instead of psychophysical harmony between the experienced order of the room and the corresponding physiological configuration, there are amazing discrepancies: the spatial ones just discussed, and the temporal one mentioned earlier. While we actually see one segment after the other, we conceive the halves as belonging to each other simultaneously. Our recognition of a room as one whole structure at rest is apparently at variance with physiological facts, not in accordance with them. So we are once again faced with the original question.

The answer has not to wait for the discovery of something radically new. But it does demand the courage to return to the oldest wisdom and to acknowledge, with all its consequences, a truth known to everyone but rejected by science. Stated in its simplest form, the truth is this: In seeing we see something visible. This statement, I am afraid, comes as an anticlimax. Your reaction might well be expressed through the words of Horace, "Mountains labor and bring forth a ridiculous mouse." To make things worse, the statement sounds like a dubious application of Husserl's concept of intentionality. Yet this apparent truism makes a bold claim. It describes seeing as an activity through which we attain an object without changing it—an action without a corresponding reaction. The statement implies that the relation connecting subject and object in sensory experience cannot be interpreted as the interaction of two bodies. Our everyday conviction that in seeing we apprehend things but nevertheless leave them as they are is not shattered through scientific criticism. It is the basis for all striving for objectivity.

Our maxim describes seeing as an activity. At the same time it refers to something visible—that is to say that things appear to us, that they manifest themselves as they are. Now *we* are the recipients. The object dominates the scene. It affects us. We can see it; we must see it. We are convinced that an object visible to one must under comparable conditions be visible to all. What *I* can see and hear, my neighbor is expected to see and hear—neither less nor more. Dissenting is received with skepticism. Surfeit is an indication of a deception of the senses. The dissenter is judged as nearsighted, agnostic—even hysterical. And is it not our criterion for hallucinations that someone sees things, hears voices, feels currents, which others cannot see, hear, or feel?

Psychiatric practice is a segment of everyday life ruled by an axiom which is never challenged but therefore also never explicitly formulated—that we meet the other one as a partner in a world which we have in common. Observers are exchangeable. One goes, the other comes and occupies his position over against something visible. The grocer and his customer who exchange goods for money are convinced that the same dollar bill visible to both of them changes hands. The grocer and his customer do not share stimuli; they do not exchange muscle contractions; their brains do not communicate with each other. The visible thing must be a third party in relation to the two observers.

So we have finally reached the point where we can announce the fundamental characteristic of sensory experience: In sensory experience a living organism is related to the Other as the Other.

The term "the Other" must be understood in the widest sense. It refers to the other one, our fellowmen just as well as to other things; the environment and finally the world. In order to avoid confusion it might be better to use the special term the Allon, derived from the Greek word signifying "the other."

The relation to the Allon, self-evident in sensory experience, thwarts discernment—for good reasons. In lieu of a full account, I will post ten theses and add some comments.

III.

(1) We meet the Allon in direct encounter, not as a ghost who sneaks into our chamber of consciousness from an outside world. The relation to the Allon is reciprocal. We move on the same level of reality.

In our macroscopic world things are our partners which respond in their own manner, resisting or supporting our intentions. We put our feet on the ground and find it solid and safe, or swampy and treacherous. Many are inclined to believe that such anthropomorphic interpretations are secondary, grafted upon an initially realistic appraisal. But even today Western man gives proper names to rivers, winds, and mountains. The Alpinist who climbs the Matterhorn does not waste his energies on a heap of granite crystals; he wants to conquer that mountain rising before him in its individual grandeur. Even scientists tell us that sense organs receive information, that nerve fibers convey messages, that effectors respond to stimuli. The discovery of a world of faceless objects is late and never complete, and it is extremely painful when it occurs as an unreflected experience, as it does in cases of depersonalization. There the original partnership with the Allon is cut asunder. Stimuli have not changed, but the I-world relation has. The patient continues to hear and see things, but he and the visible world no longer belong together. The individual knows the world as if it were seen on a floor plan, without any perspective in space or time. Seen by a depersonalized patient, space is deprived of depth. Much effort has been expended to detect the cues which determine the apprehension of the third dimension. But depth is not a purely optical phenomenon. It is relative to a mobile creature who can reach out to points "over there" from its egocentric position. Loss of depth, thus, refers to a loss of potentialities for action.

(2) The Allon is accessible to us; nevertheless it remains at a distance. It reaches us, but it must not be absorbed like stimuli, nor digested like food. The moment we make it completely our own, or surrender completely to it—as in sleep, renouncing our position opposite to it—it ceases to be the Other. Stimuli do not exist apart from the receiver's organism which they excite, but the objects of sensory experience do. The relation to the Allon implies and demands a degree of mutual independence. Sensory experience is intrinsically linked with mobility. It can only occur in a creature capable of rising up from the ground and opposing the whole to which it belongs.

The Allon in the dialectics of revealing and hiding remains enigmatic. Disease estranges us even from our own bodies; falling sick, we discover the power of the Allon in ourselves. Distance, in spite of the most intimate contacts, is a general characteristic of sensory experience. The Allon, though manifest on its surface, is unfathomable in its depth. On their surface things are well defined, clearly shaped, precisely localized, but their core eludes comprehension, description, demarcation. It keeps its secret like the other one who, should he express himself with unrestrained candor, should he "be closer than breathing, nearer than hands and feet" (Tennyson), will remain at a distance. Desdemona's oaths could not convince Othello. Jealousy has its roots in the unresolved ambiguity of the Allon. In schizophrenic experience the balance between the open facade and the hidden core is disturbed; its presence is felt in its overwhelming power.

(3) The Allon is apprehended in its suchness (in traditional terminology, in its secondary and primary qualities). We see the Empire State building in its substantiality; we do not incorporate it materially. But this unilateral relationship to its suchness is mediated by physical agents. The stimulus does not cause perceiving. Its function can be compared to that of a catalyst which initiates the actuality of sensory experience. The stimulus delimits what will be seen and determines that it will be seen. From this point of view intentionality of vision and causality of seeing are fully reconcilable.

Physiology and objective psychology acknowledge only the causal relation. They do not recognize a principal difference between suntan and sight. Just as the skin reacts to light with the production of pigments, so, supposedly, does the nervous system react with a motor response to photic stimulation. Perception, it seems, is but a dispensable by-product; it is not the genuine correlate to retinal excitation. Behavior is de-

termined by the relation of input and output; it is not understood as the relation of an experiencing being to his world.

Perhaps the following considerations may serve as a warning signal and start a critical re-evaluation. Whenever an observer studies a human subject or an animal, then, man as well as rat, the material used as stimulus and the motor responses, all must be considered as stimuli acting upon the OBSERVER'S nervous system. According to behavior theory, they must be followed by the observer's motor responses. Of course such motor effects do not know anything about the afferent impulses which released them. The output simply follows the input in time. The observer, however, actually relates the re-sponse backward to the stimuli, against the arrow of time. Unfortunately, stimuli cannot be observed, because, by definition, they are physical agents without visible or any other "secondary" qualities. They cannot be manipulated; for the physical agent when turned into a stimulus no longer exists apart from the receiving organism. Those stimuli which provoke responses in the experimental animal never reach the eyes or ears of the observer. Stimuli cannot be shared by two organisms. Stimuli and objects are not synonymous terms; stimuli are constructs, never immediate objects of experience.

(4) The relation to the Allon, though one of mutuality, is not one of equality. The Allon is the encompassing whole. It presents itself in fragments only. The actual situation is but a segment of a larger one, a part which, with open frontiers, borders on the next one. The whole is not a composite of originally solitary elements, like sensory data, impressions, bits of information.

(5) The relation I-Allon unfolds in a temporal continuum. The fragments of the Allon do not follow each other like slides projected on a screen where one has to be removed to make room for the next one. The present moment is but a focal point within the horizon of time, expanding into the future and the past.

Time is not experienced as a sequence of now-points. The actual moment is a phase in my state of becoming. In a sentence words follow each other. The phonemes recorded on a tape follow one after the other; each one is strictly separated from the other. But in listening to a speech we understand the words as parts of a whole deployed in time. The first word opens the sentence, pointing forward to those still to come. The grammatical subject will be defined by the predicate that follows, the end referring back to the beginning. Yet this temporal sequence of words is apprehended as a whole presenting one definite meaning.

(6) The present is pre-possessed by that which is not yet. The future is imminent, but we do not know what the prospects are. We respond to the precarious condition with searching, exploring, questioning. Dread is coeval with the actual situation which is emotionally charged, threatened by the unknown, the unfamiliar and the impending. Endless efforts are made to explore and to forecast, to conquer, or to pacify the Allon. In general, guided tours are preferred to the hazards of an adventurous trip. In spite of all exertion, the dreadful remains omnipresent. Witness the agoraphobic who succumbs to its presence whenever he leaves the sheltering walls of his home and finds himself exposed to the incomprehensible immensity of the Allon. The tendency to consolidate and to tighten the defensive walls has its counterpart in the propensity to transcend the border and to enjoy the wider views—the penchant towards self-preservation has its counterpart in the striving for self-realization.

(7) Every part, incomplete in itself, is capable of and in need of completion. The actual situation points to something else which is not, no longer or not yet present; it points beyond its borders to the other parts and to the whole to which it belongs. The actual situation is not closed in by iron boundaries separating the given from the void.

Here I believe we can return to our initial problem. We wondered how one could represent a room on a floor plan as a whole, although in apparent contrast to direct experience. Now, it seems, the problem has been dissolved rather than solved. The simple reason is that we experience the part as part, as capable of and in need of completion. Experience alone can teach how the unseen sectors of a room will look in particular. That the actual situation is but a fragment makes experience possible.

Many questions still remain unsettled, for instance, how the physiological error, the reversal of sides and the temporal parallaxis could be corrected.

(8) As happens so frequently in our field, the first and probably the most difficult task is to discover the problems hidden by familiarity and by the facility of practice. No one pauses to marvel that we recognize a room as the same whether we turn to the right or to the left. The sequences a, b, c, d and a, d, c, b lead to the same result. We take it for granted that the

walls seen one after the other co-exist. We are not surprised that one passing a street in the morning recognizes it as the same street at night. Not only does he recognize it as the same, but he also recognizes that the street is seen in different perspectives, that the same "what" appears in different aspects of suchness. Finally, he is aware that his own position in relation to the street is turned in the opposite direction. In everyday life, we are not surprised, but the scientist has good reason to wonder for there is no correspondence in the organization of stimuli and engrams to this experience. Yet the classical theory of sensory experience is committed to the postulate that experience is strictly correlated with physiological events.

The traditional interpretation of sensory experience does not acknowledge the I-Allon relation. It never even considers the relation of an experiencing being to things experienced. It eliminates its real topic before it starts its discussion. Instead, traditional theory interprets sensory experience as the result of the interaction of two bodies. The sender produces in the recipient a phantom-like perception. Such sensory data do not belong to the outside world of objects; they represent them—it remains unclear how and to whom. In any case, while they represent an object, they are cut off from the outside world; they are said to be subjective; they belong to the subject. Since the perceptions represent the outside world but belong to the subject, they cannot be an object of action. Every one, supposedly, carries in his consciousness a private gallery of such shadow images. The collector himself is not a part of his collection. He owns it; he has it; he does not belong to it. Sensory experience in classical theory does not include the experiencing being. The content of sensory experience is reduced to the appearance of a more or less distorted replica, a counterfeit of the outside world. Seeing is acknowledged as a physiological process, but not as the relation of seeing beings to things seen. The relation I-Allon is slashed. The Allon alone is left, but in a profoundly mutilated form. Perceptions are many; they follow each other in the order of objective time. They do not belong together in a meaningful context; they stick together through synaptic welding. Positivism from Hume to Skinner preaches the gospel that sense is repeated nonsense. The order and connection of perceptions is determined by the order and connection of afferent impulses and their traces. For this reason classical theory cannot tolerate any discrepancies between the order of sensory data and physiological events.

Traditional interpretation claims that the world is presented subjectively in my consciousness. The relation I-Allon implies that in our encounter with the world we see things themselves; they are our partners and we are theirs. My sensory experience includes myself, as the one who sees visible things, who is directed to them but also opposite to them.

In sensory experience we are aware of a dual order: of the order of our own acts of seeing and of the order of things seen. The two orders come into contact. They do NOT COINCIDE.

In the sequence of our always limited views, we come to understand how the fragments of things seen belong together. In this process of assembling the fragments meaningful significance provides the *Leitmotiv*. Passing from one phase to the next in a state of becoming, we apprehend the permanent order of things in their own right. We are able to detach the order of the Allon from the order of its appearance to us. In fact, our understanding of our own position is dominated by our understanding of the whole to which we relate ourselves. With the question, "What time is it now?" I order my personal now into the order of public time.

The capacity of discriminating the two orders in their mutual relation develops slowly during the years from early childhood to maturity. Not before the age of five or six will a child learn that games can be played according to rules and that things require to be treated in the same way. The Allon, lasting, resisting, demands our respect.

The relation I-Allon places each one of us in an egocentric position. From this central point space opens before us as a stage for future action. Things seen over there at this moment now, nevertheless, present themselves as possible goals.

The dual order enables us to repeat, to see things again. It makes communication possible, because the Allon opens before us as the one all-encompassing world. Limited to his store of sensory data, every one would live in a private world.

(9) In our physical existence we are confined to fragments; we can exchange only one part for another one, move from place to place, from day to day. The whole as such is inaccessible. We get hold of it through the mediation of language or other means of symbolic representation. Words are not substitutes for absent things or relations accessible to us before (the so-called) verbalization occurs. Symbolic representation enables us

to break through the barriers which are set by our corporeal existence. The word room signifies a room as a whole. A map of the United States presents to us the country as a whole in its extension between the two oceans. Discarding natural size, the map delivers into our hands the spatial order of the whole in a scale adapted to our natural limits. A map of New York, equaling the city in size, would be of no use. The natural relations are inverted. Symbolic representation gives us power over that whole of which we are but a tiny part. Yet in using a map we submit to the order of the whole and let our actions be ordered by it.

(10) In our orientation in time and space, we descend from the whole to the here and now. We determine this moment as the eleventh hour of this day, this month, and this year. We determine the actual present through its relation to a whole which is never actually given. The word "today" signifies this day in its extension of 24 hours; the dial of a clock represents all the possibilities; the hands in motion mark the actual situation. Confined to one single point of the periphery, we use the word "today," signifying a day in its full circle. While we constantly change our positions between morning and night, we mean this same whole of 24 hours: "today." Only the one who can relate the actual moment, beyond its boundaries, to the not-present whole is able to understand and therefore to remember, let us say, noontime, the luncheon hour, and the lunch.

We have made it our task to apply aesthesiology to pathology. In our efforts to account for a minor deficiency, we were forced to extend our runways farther and farther. Can we now jump higher? What are the results? The first one is, I believe, identical with the lengthy preparations themselves, which demonstrate that ease of performance is not an indicator of psychological simplicity. In fact, I have tried to show that psychopathology has to be built on a psychology which is not the psychology of an apparatus, not a physiological but a psychological psychology, if I may say so, one which studies man as an experiencing being in his I-World relations.

"Behavior and the nervous system" has been a general theme of many conferences held during the last decade. Behavior was always treated as the dependent variable. While the exploration of the nervous system was highly sophisticated, the account given of the complex human behavior which made such sophistication possible was scanty and naive. Seeing, observing, describing, remembering, measuring, predicting, all were taken for granted. To predict behavior is one thing; to understand predicting is the true psychological problem. All attempts to define consciousness or mind failed to the satisfaction of most participants. Of course, one cannot define consciousness or mind as abstract entities; however, one can well define an experiencing being as an organism capable of apprehending the Other as the Other and one can define the experiencing human being as one capable of comprehending the whole of which he is a part.

If the I-world relations are first acknowledged, it should not be too difficult to survey their disturbances. I have already pointed in passing to depersonalization, to agoraphobia, to the dysmnesic, the asymbolic, the schizophrenic. Let me add a few remarks in relation to the organic psychoses. The account given of the dual order leads directly into the psychopathology of symptomatic psychoses with clouding of consciousness as the cardinal sign. It might not be inappropriate to revive the obsolete term of mental confusion and to consider it as a manifestation of disturbances of the I-Allon relation varying in degree from the mild stages of the sub-acute delirium and perplexity, to the wild excitement of psychomotor fugues and the severe mental disorganization in senile psychoses. One could place disturbances of the I-Allon relation side by side with the familiar symptomatology of organic psychoses and coordinate them like two columns in a bilingual dictionary. In one column then, we would read about disorientation, fleeting attention, incoherence of thinking, purposeless action, and in the other one about disarray and fusion of the two orders, radical fragmentation, atomatization of the temporal continuum, the shrinking of the horizon of time, the vanishing of the whole. The APA nomenclature, enumerates impairments of orientation, memory, judgment, intellectual functions and affect as characteristic for organic brain disorder. The I-Allon relation enables us to understand the inner unity of this aggregate. Here, picking the ripe berries from the I-Allon bush we may go one step further and extend our interpretation to the optical hallucinations as they occur in acute delirium.

Under normal conditions, as long as the I-Allon relation is kept intact, we see things in relation to us, but as their own order requires. When, however, this relation is not preserved in its integrity, the physiological error, the inversion of sides, the temporal parallaxis can no longer be corrected. Under those conditions the sequences a, b, c, d and a, d, c, b cannot be identified. Im-

pressions succeeding each other in time do not coalesce into a meaningful whole. They contradict, they counteract each other. Things seen, as the eyes see them, must look derisive, mocking, threatening, bewitched. Every attempt to create order increases disorder. Stability breaks down in a whirling hypermetamorphosis. The panic-driven behavior in acute delirium and in psychomotor attacks is a dramatic manifestation of the breakdown of the I-Allon relation. In sharp contrast to schizophrenic voices, delirious hallucinations manifest directly a primary dissolution of those functions of the brain which normally sustain the I-Allon relation.

One may wonder if the conditions which empiricists consider fundamental are in fact reached only in the extreme pathological stages. In any case, the normal functions of the brain must be compatible with the sustenance of the I-Allon relation and the principles of neurophysiology should be revised accordingly. For the existential categories of relation to potentialities, of meaningful correlation, of the historical order of time, in short, of the I-world relation characterize all sensory experience.

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"Narcissism" in Psychoanalysis and the "Love of Oneself" in Existential Psychotherapy

CLEMENS E. BENDA, M.D.

A paramount problem in existential or humanistic psychology is the question: In what way is psychotherapy influenced by the new concepts of man? There is no doubt that the main impetus in modern psychotherapy has come from psychoanalysis; and psychoanalysts point proudly to analysis as a depth psychology, in contrast to other psychological approaches which are shrugged off as "surface" psychologies. If existential psychology is now claiming an even deeper understanding of man and rejecting the psychoanalytical framework of thinking, this claim has certainly to be justified.

Although this meeting is mainly concerned with the practical implications of existential psychotherapy, some brief introductory theoretical remarks are in order. It is surprising how few attempts are made to understand the framework of reference in which the psychoanalytical understanding of man operates. With the exception of Ludwig Binswanger's classical study of Freud's theory of man as "homo naturalis," friends and foes of psychoanalysis have been equally careful to avoid clarifying the philosophy underlying the practice of classical psychoanalysis.

Freud and his disciples have always insisted on the *libido theory* as a cornerstone of psychoanalytical theory formation, and differences with other analytical schools such as Jung, Adler and the Neo-Freudians (Horney, Fromm, Sullivan) have been based on a different interpretation of the libido theory. Freud himself had broken with Jung over the latter's interpretation of libido as a universal drive, as he himself has clearly outlined. His differences with Adler arose from Adler's refusal to attribute the genesis of all neurotic behavior patterns to sexual problems. Although somewhat aware of the inadequacy of his own thinking in this regard—as is obvious, for instance, from his article on narcissism, Freud insisted on the acceptance of his thinking as a basis of psychoanalysis. To the present day, belonging to the analytical school is contingent on confessing to this creed.

In psychoanalytical thinking, certain critical points in the individual's development have been considered pivotal; e.g., the Oedipus situation, which represents the critical moment in all neuroses. Neurotic and psychotic behavior are linked to certain deflections of libidinal object cathexis. Thus all neurotic and psychotic behavior patterns can be fitted into anomalies in object cathexis, the damming of normal libidinal discharge, and the accumulation of ego libido which expresses itself in primary and secondary *narcissism*.

Reading psychoanalytical case reports or perusing the literature in general, one is amazed to see that narcissism is one of the fundamental concepts in psychoanalysis. In outstanding publications down to most recent writings, the word "narcissism" appears in every paragraph as an explanation of abnormal behavior. If, therefore, narcissism can be considered the most basic deflection of normal behavior in interpersonal relations, it seems worthwhile to take this concept as a point of departure for a demonstration of the ways in which psychoanalytical thinking and the existential approach differ.

What is narcissism? All writings on narcissism in the last 45 years are based on Freud's classical paper on the subject, first published in the *Jahrbuch* in 1914. Freud explains that narcissism originally is the experience of sexual pleasure in gazing at, caressing and fondling (one's own body) until complete gratification ensues. "Developed to this degree, narcissism has the significance of a perversion which has absorbed the whole sexual life of the subject." Freud continues, that narcissism has a much more universal meaning; and he has found that a similar kind of narcissistic attitude seems to limit the neurotic's susceptibility to love. Narcissism then is a "libidinal complement to the egoism of self preservation" which may be attributed to every living creature. Freud later explains that libido withdrawn from the outer world has been directed to the ego, giving rise to a state which we may call "narcissism." This concept has led to the distinction of primary narcissism, where the individual is never able to transfer libido attached to his own body organs to objects, while libido in secondary narcissism is withdrawn from the outer world and concentrated on the own ego and its corporal representation.

From Walter E. Fernald State School, Waverly, Mass.; and Massachusetts General Hospital, Boston, Mass.

Looking at this classical paper now, after 46 years, it is almost painful to observe how helplessly Freud staggered through his own theoretical concepts in order to maintain a theory in which he attributes to the ego a primary instinct of self preservation which is not libidinal; secondly, an ego libido which then is either thrown on an object, by which procedure the ego is deprived of a part of libido, or the libido is taken back to the individual, by which measure the ego libido is enhanced and the object libido impoverished.

As Clara Thompson has made very clear, Freud assumed a quantum of sexual energy which is attached to every organ in the body. If this libidinal energy becomes attached to another organism, the "narcissistic libido becomes converted into object libido" and this is object love. But the individual has lost ego libido in this act, and Freud comes to the strange conclusion that this is "why man in love suffers from feelings of unworthiness. He has lost some of his self love, his ego is poorer in libido." Freud says: ". . . libidinal object-cathexis does not raise the self-regard. The effect of the dependence upon the loved object is to lower that feeling: the lover is humble. He who loves has, so to speak, forfeited a part of his narcissism, which can only be replaced by his being loved. In all these respects the self-regarding feelings seem to remain in a relation to the narcissistic element in the erotic life." As a compensation, however, some libido is returned to him from the other person, and his self esteem may be restored. Should the object libido be rebuffed or frustrated, the libido returns to the individual and becomes attached to his own body as a secondary narcissism.

Needless to say, the shifting of libido between ego libido and object libido and the different forms of deflections into fantasy formations, narcissism and ideal ego permits the libido theory to be the basic conceptual framework into which can be fitted every neurotic and psychotic anomaly. The sick person withdraws libido from objects and indulges in narcissism to ease his pain. When the illness has passed, the patient is again able to project himself into object-cathexis. The "ideal ego" is said to derive from the narcissistic perfection in childhood, and Freud assumes that the ideal ego may be directed to "self love which the real ego enjoyed in childhood." The libido is unable to "overcome the narcissistic perfection" of childhood. From this switch-yard is derived the concept of "sublimation," by which the instinct is directed toward an aim "other than and remote from sexual gratification." "Sublimation is a way out, a way by which the claims of the ego can be met without involving repression."

As a further step, Freud arrived at an explanation of *conscience* as a "special institution in the mind which performs the task of seeing that narcissistic gratification is secured from the ego-ideal and that, with this end in view, it constantly watches the real ego and measures it by that ideal." In the framework of the libido theory, the superego or ego ideal is also charged with libido. "Large quantities of libido which is essentially homosexual are in this way drawn into the formation of the narcissistic ego-ideal and find outlet and gratification in maintaining it."

These few remarks must suffice to clarify the way in which the libido theory of Freud forms the scaffolding of the whole psychoanalytical understanding of man's emotions and relations to the outside world. The significance of this theory rests on the fact that not only the actual emotional life (in Freud's term, the libido cathexis) is here included, but the theory is supposed to provide an understanding of the superego, conscience, sublimation and thus creativity as well as love.

Narcissism plays a paramount role in all psychoanalytical writing. The great theories of the school, from Fenichel and Wilhelm Reich to Heinz Hartmann, have dealt extensively with interpretation of the libido theory and have attempted to maintain it as an essential part of psychoanalytical thinking. On the other hand, those schools which have branched off from orthodox psychoanalysis (Karen Horney, Fromm, Sullivan, Clara Thompson, and several others) have focused attention on the inadequacies as well as the contradictions inherent in the libido theory.

Many of the thinkers, psychologists and psychiatrists who are referred to as existentialists or humanistic psychologists are dubious as to whether a new understanding of man can be fitted into the old garment. The libido theory with its implications seems not only inadequate but erroneous, distorting a large number of actual observations as well as pressing the material into a framework of interpretations which obviate a real understanding of man's totality. I personally have always maintained that the main contribution of depth psychology—the understanding of the dynamics of the id—is unsurpassed and still valid, but the development of psychoanalysis into the so-called "ego psychology" with its three types of *mental apparatus* is unacceptable and cannot be modified into an understanding of the self.

Narcissism (whatever the scientific connotation may be) is essentially a "self love," an egotism or selfishness which has a definitely derogative connotation. Narcissism implies that the ego loves itself and is therefore unable to love others. It implies further that narcissism is an enhancement of the ego which therefore should at least produce perfect human beings who may not waste love on others but must strive toward that self-perfection which seems the goal of all western civilization. Freud—strangely enough—believed that we possess "narcissistic perfection" in childhood but lose it through our frustrating and rebuffing contacts with the outer world. Yet narcissism is in moral terms a sin, in psychological terms a deflection or even perversion, and in human terms a selfishness which is highly objectionable.

All psychoanalytical therapy is faced with the task of inducing the narcissistic subject to give up some of his narcissism, impoverish his own libido, and again succumb to object-cathexis. Yet why should one forfeit pleasurable self perfection in the service of object devotion if and when one has reached a much more desirable state of independence while the emotional returns from the outside are—to say the least—questionable, unpredictable, unreliable, and so often withheld? Why again expose the individual to the hazards of rebuff and deflation if in secondary narcissism he has reached the final goal, having recovered from frustration and debunking and reached a new state of self-assurance whereby his ego is fortified against the hurts of the changing outer world?

While psychoanalysis is confronted with the problem of changing narcissism into object love, modern society is faced with a similar problem in its endeavor to create better interpersonal relations and a sound, healthy community. The great amount of frustration, the increased hostility and competitiveness, the lack of love and consideration have been noted as characteristic features of our modern world.[1] Love is considered the last resort to bridge the aloneness, isolation and anxieties inherent in modern life. And man is again reminded of the word of the Bible, standing in the center of Western tradition: *Love thy neighbor as thyself.* While this word seems to take it for granted that everyone loves himself and requests that this same love be extended to one's neighbor, apparently the deeper implication is that you are doing well if you love your neighbor as much as yourself. It means also that you cannot love another person unless you love yourself, and the measure of love is gauged by the amount of self-love. Religion evidently does not ask the individual to forfeit his self-love and actually implies that the ability to love others hinges upon the ability to love oneself.

We are facing the strange situation that self-love is considered a basic value and requirement. The question therefore arises: Is this self-love identical with the narcissism of psychoanalysis? Is it identical with the egoism and the concupiscence of the Christian tradition in which the individual is taught that self-love, "selfishness," is the source of all evil and one should give up the self in order to surrender to others? Our Western civilization shows an unusual degree of fragmentation, self-destruction and hostility of all against all, and this pattern has gathered momentum with every decade. Is the inability to love, to respect, to accept others caused by the self-destructiveness, self-hate and self-rejection which we are able to trace in the analysis of so many persons? Is this state of mind the result of our Western tradition which has prevented us from due consideration of our own self?

If psychiatry, religion, sociology and other disciplines concerned with culture and mental health have joined forces in the search for a new emotional climate in which love has found a central place, it is apparent at the same time that the Judaeo-Christian religion and psychoanalysis have endangered the very fundament of love —the acceptance and love of oneself, and we must look for a new framework of mind that will enable us to view the problem with a fresh approach.

There is no doubt that the phenomenon of self-centeredness, selfishness, egotism or "narcissism" can be frequently observed. Time and again we see that an individual is concerned only with his own needs and gratifications. He has little ability to care for and to be concerend with other persons and to extend affection, empathy and love. The phenomenon of self-centeredness and narcissism is a basic observation in mental illness and appears to underlie a number of deflections and deviations in human interrelatedness. But does this "narcissism" rest on a loving concern with oneself? Are the emotions not flowing toward others and the outside world because of being bottled up by self-love and a pleasurable attention to one's own ego?

We have three sources of information with which to test the validity of the libido theory:

[1] C. E. Benda: "Der Mensch im Zeitalter der Lieblosigkeit." *Steingrüben Verlag,* Stuttgart, 1956.

1. Now that psychiatry has moved from observations on adults directly into the child's world in health and under abnormal conditions, we have a wealth of data indicating that the child's experience is by no means one of omnipotence and of happy concern with himself. The child develops in complete dependence on the world around him, and his original relatedness is a state of symbiosis rather than a primary isolation. Out of a symbiotic existence, the child's self is gradually individualized. His experience is that of a physical, emotional and mental dependence and inferiority, and his ego development is a slow process of recognizing and learning to use the facilities within his own power.

2. Time and space do not permit a discussion of the data on childhood schizophrenia and childhood autism,[2] wherein the formation of a separate ego structure is deeply disturbed. There is definite evidence that the lack of personal interrelationships is not due to a primary narcissism but to a failure or loss of contact in the emotional matrix of ego development.

3. Analysis of self-experience in those conditions which are termed "narcissism" reveals that, in contrast to self-love and pleasurable satisfaction, the basic phenomenon is dissatisfaction, conviction of failure and inadequacy, and self-hate. The narcissistic person does not stay in contact with and show loving concern for others. He has been thrown back on his own personality on account of isolation, inability to cope with the demands of the outside world and his own demands in counteracting the pressure and stress under which he is forced to live. The inadequacy of psychosomatic self-expression leads to self-hate and destruction but at the same time to an oversensibility to all other influences which have to be fenced off.

It is the *framework* in which man experiences himself and his existence that is of decisive importance. While the natural science approach tries to *explain* the human experiential world by an evolutionistic theory of instincts and their vicissitudes, existentialism recognizes the trilogy of the human world. None of the three spheres can be derived from the others and explained by the laws which are valid in another field. Each sphere represents a different aspect of the unique mode of human existence:

1) Man is embedded in an environment with which he interacts in the biological terms of living—the world of matter, metabolism, and biological exchange. This sphere is the subject of the "natural sciences": physics, biochemistry, biology, some of the social sciences; in brief, every aspect of which objective data can be collected.

2) The sphere of the contemporary world with which a human being interacts in living contact. The emotional currents flow within the animated world and place each organism in a field of psychic interrelationships which form an intricate meshwork of mutual influence.

3) The inner world of man: his imagery, dreams, aspirations and thought; in brief, the universe which is individual in each person and can be shared with others only through the inadequate channels of communication.

Far from being separate worlds, however, it must be emphasized that all emotional and mental contact with reality occurs through the imagery by which reality is represented. Feelings and emotions are not related to objective facts but represent the emotional climate in which man acts according to the images which he has formed of his situation.

Rollo May has recently outlined the same train of thought in a very illuminating article on existentialism. Here he gives a classical demonstration[3] of the three modes in which man lives, in an interpretation of Binswanger's thoughts:

> First, there is *Umwelt*, literally meaning "world around." This is the biological world, generally called "environment." This is the world where natural law is sovereign, the biological world of drives, instincts, and deterministic forces, the finite world, the world in which the terms "adjustment" and "adaptation" have valid meaning (the individual and his surrounding environment).
>
> Secondly, there is *Mitwelt*, literally "with-world," the world of one's fellow men, of interpersonal relationships. In this world the term "relationship" comes into its own. For the essence of relationship is that both persons are always more than objects to each other, and, in the encounter between them, both are to some extent changed (the coexistent, contemporary world).
>
> The third mode of world is *Eigenwelt*, or "own-world," the mode of self-consciousness, unique to human beings (man's inner world).

There is no opportunity to dwell in detail on the structural aspects of man's existence. I may only stress that human experience is not primarily unconscious and then censored, and a certain amount of it admitted to consciousness as an aftereffect. Human experience—from birth on—is the outcome of contact with the world, and all experience is filtered to the individual through a screen of interpretation. The individual encounters the world around him through evaluations, interpretations, and selective choices. Therefore, all feelings occur in a framework of

[2] C. E. Benda: Childhood Schizophrenia, Autism and Heller's Disease, 1960, pp. 469-492.

[3] R. May, Amer. Handbook of Psychiatry, p. 1355.

reference of evaluation and cultural choices and are not due to unconscious emotional contacts alone. The formation of man's experience of himself, of his own body, of his own reactions and aspirations, of his own individuality is a slow process of growth which can be achieved only through comparison of one's own universe with the universe around us.

Having neither time nor space to deal with the structure of the self, the essence of being and existence when we are mainly concerned with psychotherapy, we must focus attention on a point which has been too much neglected in therapeutic practice.

Psychoanalysis as a "depth analysis" is concerned with emotions and unconscious dynamics, and secondarily with ego-defenses. Through dreams, slips of the tongue, and other unguarded manifestations of behavior, we may find a way to catch glimpses of the actual forces within our emotional unconscious life. But as soon as the unconscious is translated into conscious knowledge, awareness and understanding, and feelings and experiences are communicated through human language, they lose the immediacy of experience and are pressed into common patterns of communicable goods of exchange which by their very nature are foreign to the world of personal experience, the Eigenwelt of our imagination and thoughts.

In this process of sharing experience in psychotherapy, much of the actual nature of experience and emotions is lost. All psychotherapy has to work essentially through the medium of language and interpretation while the personality of the therapist must remain in the background. If, however, the intellectual interpretation of experience in psychotherapy is only a part of the therapeutic situation wherein two persons meet and the therapist attempts to change the framework of thinking and feeling in the person who entrusts himself to the therapist, we must reconsider the therapeutic process and investigate the actual forces which contribute to therapeutic success.

In the framework of analytical thinking, consciousness is the aftereffect of the unconscious mind. It is the registration board of feelings, drives, needs and emotions. This is a one-way traffic from the primary unconscious experience to the aftereffect of awareness and consciousness. However, the self is in the process of becoming from the very beginning. Experiences are determined by human relationships, by the Mitwelt which exists at the same time. Consciousness is formed through communication. Language is in action from the very first day of being. Thus consciousness is not an aftereffect of pre-conscious experience but its structure determines the modes of experience and therefore the world in which man lives.

Psychotherapy cannot use forms of human emotional exchange open to a loving relatedness and emotional interaction: psychotherapy by its very nature is restricted to the communication of thinking and interpretation of the world, reenforced by the personality of the therapist. Any therapeutic success depends on the communication of a new framework of reference which the patient is willing to accept and through which he replaces his own form of experience by a new mode of being.

If we consider the mental "illnesses" of this world as ab-normal modes of existence which impair and impoverish the range of human experience, we realize that the subject of psychotherapeutic endeavor—forms of sexual deflection and aberration; modes of fear, dread and anxiety; forms of compulsive behavior patterns—are modes of restricted existence in which large areas of human experience are excluded from access to the self. Successful therapy breaks the bars of the prison in which the self is caught, and opens the gate to new experience that was inaccessible before therapeutic help was endorsed.

Applying this thinking, for instance to the restricted area of narcissism, we gain a new understanding of the situation. While narcissism is said to be the source of inability to love and the cause of deflections of sexual behavior like homosexuality and impotence, narcissism, far from being a love of oneself, turns out to be a restriction upon the self, due to the inability to form any contact with the Mitwelt. Thus not a positive love of oneself but the negative aspect of absent contact formation and human interaction is the basic phenomenon; and therapy has to deal not with a person who loves himself but with a person who has lost much of his human contacts and is unable to transcend his own self in human relatedness with others. The love of oneself turns out to be a last retreat upon an inadequate, helpless and hate-worthy center which has fallen short of one's aspirations and hopes and remains as the last remnant of life and existence.

I would like to illustrate the point with two representative case histories.

Case No. 1. The patient is a 24-year woman, married six months, living in a congenial and happy atmosphere. There has been no indication in the course of analysis that this is not so. She is an artist, unusually good looking and attractive, the

only child of religious Protestant midwestern school teachers who were 35 and 40 when the child was born. The home atmosphere was strict, almost sectarian and over-protective. The child developed early anxieties. Attending kindergarten and first-grade was associated with psychosomatic symptoms of stomach trouble, vomiting, anxiety and extreme fear. Even at that age she worried greatly and had strange thoughts; for instance: "What if mother had killed grandmother?" (who had undergone extensive surgery). Parental attention was concentrated on preventing association with boys: one is a "good girl" if one does not show affection for boys. Girls who were interested in boys were marked as "boy crazy" and this term was one of the most severe criticisms in the home vocabulary.

As a result of all this the girl felt safe only when within the circle of her girl friends and she avoided contact with boys. At the same time the parents instilled in the child's mind a sense of her great value. She was too good for this or that one, and any boy who dared visit the home or tried to date regularly was driven away by suspicion and unfriendliness.

When the girl entered college, she was timid and retiring but self-reliant. She kept away from aggressive boys and was attracted to artistic, esthetic students who also avoided any libidinous aggressiveness toward their dates. She was at the same time the subject of several emotional cross currents. The boys to whom she felt attracted were called "homosexuals" by other boys and by some women, and some women undoubtedly felt a certain attraction to our patient. Finding herself amidst these emotional currents, her worry about becoming a homosexual herself gained compulsive power and she developed tremendous anxieties and obsessive thoughts. She avoided being seen with other women or even sitting on a chair previously occupied by another woman. She also withdrew from many contacts with male students but felt attracted to one very artistic co-student who was considered "queer" by some classmates and teachers.

In contrast to these people, her prospective husband was a man of unusual intelligence, masculine persistence and tenderness, who had made up his mind to marry this girl and continued his courtship over several years despite all rebuffs and separations. The parents' hostility toward the boy and her dependence on the parents went so far she once returned the boy's engagement ring because the parents did not approve of the match. It was not until several months later, after graduation, that she found the strength to again accept the ring and tell her parents that she would marry this man.

Although happily married, her anxieties persisted during the first six months of marriage: she was afraid that she might be homosexual. With extreme uneasiness she watched her contacts with other women, especially those who seemed somewhat "masculine," and she examined herself meticulously to see whether she felt any attraction to them. In reality, it was her fear of being considered homosexual which was the basis of her disturbance.

In an analysis of the case, the main problem was to evaluate whether her anxieties were actually due to some latent wishes and tendencies, as the libido theory would suggest, or were *thought-processes* which derived from the idea that others could consider her homosexual and therefore abnormal. It became quite obvious in the course of analysis that we dealt here with thoughts and not drives, and that it was the conscious personality who in her dependence on others could not handle the reality situation. In a psychotherapy dealing with her imagery, dreams, day dreams and thought processes, it became evident that the constriction of her inner world was the cause of her anxiety and helplessness. Once she had learned to understand the influence of her parents' thinking on her own thoughts and liberated herself from a slanted and warped outlook on the world, she lost her compulsive thinking and became free and outgoing and had very satisfying emotional contact with male and female alike.

Case No. 2. This case concerns a man who was an illegitimate child born in a small and old community in Continental Europe. His mother, a religious Protestant woman, belonged to a narrow, intolerant sect which considered sex as sin. The father was a rich business man, an esteemed and reputable member of the community, in whose family service the mother had been when the pregnancy occurred. As tradition in these old world communities indicates, the mother was a "fallen" woman; but she redeemed herself through her extremely religious, pious life as a respected member of the community. Neighbors would never let her forget her sinful past, however, and would pointedly ask: "How is your son, *Miss* Johnson?

The son grew up in an atmosphere of suspicion, looked upon as a bad seed who would never amount to anything. He was a handsome boy with superior intelligence and even his teachers would remark that it was too bad he was so intelligent; as an illegitimate child, he had no right to be handsome and smart. His activities were watched with distrust; and not only was he more severely punished than others for common boyish pranks, but each act was considered a new proof of his inherent badness. "Don't become like your father," was the constant admonition of his mother, and such remarks were unfailingly accompanied by threats of placement in an institution or orphanage in case of any relapse. Needless to say, sexual maturity at the time of adolescence became a constant source of anxiety. To fall in love with a girl and be caught in love making or even play would mean definite condemnation and proof of his original sin.

In his self-experience, this man was thoroughly convinced that he was not good enough to aspire to a beautiful wife, to feel desire and love and to strive for a career equal to his intelligence. He finally married a good and rather unattractive woman, several years his senior, who also came from a religious background, and both were united in their ideals.

When after many years of marriage this man developed enough self-confidence to engage in the pursuit of an academic career and found himself to be a good looking, strong man, his marital relations became more and more precarious. During times of long separation, he gave in to some homosexual activities in which he played a rather passive role but which to him seemed to prove that he was actually abnormal, inherently bad, and deprived of all redemption.

It is characteristic of this person that when I asked whether he ever thought of striking up a friendship with or making love to other women, he almost horrifiedly replied that this was a mortal sin and he would have to commit suicide if he were guilty of such wrongdoing. It became clear in the course of analysis that in increasing maturity and liberation of his prejudiced inner world to a greater freedom would endanger his marriage to such an extent that he would probably fall in love with some young and attractive woman whom he might desire. In order to avoid such an issue, the homosexual activities not only served the purpose of a guilt-free relief of sexual tension but at the same time reinforced his moral sense of condemnation. In being deprived of redemption, he had a

right to be an outcast and rebellious and at the same time stay within the fold of external morality in which he was not guilty of the sin of adultery.

This case is especially illuminating in demonstrating the influence of the cultural, moral and religious framework on emotional experiences. It is obvious in these histories that it is not early infantile experiences of the Oedipal or pre-Oedipal period that are the source of deflections of human contact formation; the spiritual framework in which a child grows into adolescence and adulthood is the decisive factor under which a personality is molded. Each of these cases reveals a dysrhythmia in emotional development. The inhibitory influences of the cultural setting delay maturation and preserve infantile and juvenile attitudes beyond the time of their justification and usefulness. Such persons enter new stages of development, "immature" and unprepared for the requirements of the new period. Obviously the psychotherapy which deals with these conditions must not only remove the obstacles to emotional ripening but at the same time must provide a new framework of spiritual and emotional experience, so that the person is prepared to cope with his existence.

In existential psychotherapy, the interpretation of each case requires an individual approach and a shifting emphasis to certain aspects of the inadequate contact formation with the world. It is obvious that an existential interpretation of man's world cannot use the libido theory as an explanation of man's difficulties. While narcissism seems to be the source of inability to love in deflections of sexual behavior, far from being a love of oneself it is a restriction upon the self of the ability to form any contact with the Mitwelt. Thus the basic phenomenon is not a positive love of oneself but the negative aspect of absent contact formation and human interaction. Therapy has to deal with a person who has lost human contact and is unable to transcend his own self in human relatedness with others. The "selfishness" is the last retreat upon an inadequate, helpless and hate-worthy center which has fallen short of one's aspirations and hopes.

One is tempted to say that the person has to learn to accept himself, but on second thought this formulation appears inadequate. In the patient's experience, to love a person so unworthy of love means to give up all ideals and self-respect. Such a suggestion is resented for two reasons. If insight into one's own world reveals inadequacy and failure, acceptance of this situation would mean foregoing one's aspirations and goals in life. Such resignation is unbearable. But even the love of another person is resented because of the feeling that the other person does not know him and is either projecting some ideals or wants to use him for his own purposes. This is unacceptable.

Thus the psychotherapeutic "encounter" cannot be described in general terms such as "love," "assurance," "acceptance" but must analyze two aspects of the patient's abnormal mode of existence. In striving for a true understanding of his feelings, the classical analysis is most helpful in hurdling the defenses, resistance, repressions and devices with which the patient justifies his reactions. It is surprising to see how many persons with homosexual tendencies resist therapy and insist that their difficulties are a constitutional, genetic or psychosomatic anomaly with which they were endowed and about which nothing can be done. Psychoanalysis often spends years on patients to reveal that their paranoid reactions, frigidity, impotence or anxieties are due to "latent homosexuality." Thus this deflection is a "basic phenomenon" which is thought to explain the anomalies. Such procedure reinforces rather than eliminates the experience of pathology with which one has to live.

An analysis of the actual emotions and feelings of the patient will usually reveal that the framework of his experience is warped and he evaluates his own situation as well as the world in which he lives in an abnormal manner. Hence psychotherapy has to deal with the inner world of the patient: his thinking, dreaming and imagery.

In therapy, we attempt to change the two complementary aspects of experience: the imagery reflecting our concepts of the outer world and our own position in it, and the self-experience in which we evaluate our self and place it in the power field of human relations.

As far as the imagery is concerned, the classical approach (dream analysis; analysis of day dreaming and fantasy work; analysis of behavior, attitudes, and physiognomic expressions) provides an understanding of the unconscious. In contrast to the psychoanalytical attempt to explain this inner world through libido dynamics, existential psychotherapy collects and appreciates the wealth of phenomena without a premature evaluation of what is and what is not important. Since each phenomenon has its own meaning, the whole field of phenomena must be grasped and understood rather than explained. In the process of interpretation, it will become obvious to the patient that he actually lives in an impoverished world from which he has excluded large areas of possible experiences because they are a threat to

his personality or he feels unable to cope with them.

In considering the individual's position in the power field of human relationships, we find that what is considered a narcissistic retreat and love of oneself, turns out to be the experience of unworthiness of love, of self-rejection, hate and inadequacy. Therefore Narcissus, who in the Greek myth fell in love with his own reflection which he saw mirrored in the water, is indeed no symbol of the state in which the unhappy patient finds himself.

Going a step further, we realize that the person who hates himself is unable to enter into a loving relationship with another. He will either enter into an encounter with wrong expectations which are bound to lead anew to disappointment and frustration, or he will be unable to throw himself into a new relationship and remain passive, isolated and without initiative. He is doomed to failure in either case, because the "we" experience is a matter of give and take in every relationship. The beggar who has nothing to give and can only take will find himself expelled sooner or later from any company.

The analysis of expectations is a matter of importance. In man's expectations are reflected his anticipations and needs, and an individual meets the world in a framework of expectations which determines his successes as well as the type and amount of frustration he is bound to suffer. It has long been known that most "neurotic" persons have a low threshold of frustration. It may be because of the wrong expectations with which they approach each new relationship that they suffer so much greater frustration than the average. The individual in love who is demanding and puts the other person above himself will one day find out that no human relation can last if entered into under such unequal conditions. He who considers himself inadequate and unworthy of love will soon look for a justification of this isolation and, viewing the world with hostility and hate, project his aggressions into the outer world.

The individual who is convinced of his own shortcomings, failures and defects cannot fall in love with himself or with others, and humble acceptance is not the simple answer. He can enter the field of human relations as an equal partner only if he realizes his own uniqueness and learns to see his own being in all its complexities as a source of experience and creativeness. Especially the sensitive, creative person—who is most likely to complain about rough reality—may grasp that his own delicacy provided his perceptual world and may learn to appreciate that what first seemed a deficiency is an asset. It is thus the person whose self-experience reveals himself as the source of all creative powers who may accept and understand his own uniqueness; out of this understanding may come a comprehension of what he can contribute to the world. In the deep respect which comes from self-understanding, one can see the other person not only in his limitations and shortcomings but in his unique wholeness, and one may treasure the relationship to another person to whom one is bound in love.

Thus, in contrast to the negative concept of narcissism as selfishness, egocentricity and egotism which require self-abnegation, we realize the depth of the words: Love thy neighbor as thyself. Self-acceptance and self-enhancement are processes of constant growth and becoming, the only firm fundaments of a sound and creative relationship to the world in which we live.

Summary

1) One of the main problems in existential psychiatry concerns the question of whether existential thinking alters the procedure of classical psychoanalysis in psychotherapy and, if so, in what way.

2) In psychoanalysis, Freud's libido theory maintains a central position even if modern psychoanalysis has moved from depth-psychology of the unconscious to ego-psychology and the exploration of ego defenses.

3) Since *narcissism* plays a fundamental role in all anomalies of object love, problems of narcissism and egocentricity seem well suited to point out the differences between psychoanalytical interpretation of anomalies in interpersonal relationships and the new existential approach.

4) All modern writing on narcissism is based on Freud's classical paper on the subject, published in 1914. Some of his basic thoughts are reviewed.

5) Far beyond the psychoanalytical interpretation, the problem of narcissism and human "selfishness" is important on account of the fact that the Judaeo-Christian religion as well as anthropology and sociology deal with the necessity of love to overcome the increasing hostility and frustration in modern life.

6) In psychiatry, *narcissism* is found a fundamental phenomenon in childhood autism, schizophrenia, many psychoneuroses, homosexuality and phenomena of neurotic withdrawal from the outside world. In all these disorders, analysis

reveals the inability to love another person (to achieve "object-cathexis"). Narcissism with its pathological manifestations—as homosexuality, latent or patent, paranoic reactions, anxiety and guilt—is thus in the center of ego-defenses in all deflections of love and sex.

7) Modern existentialism does not attempt to consider the phenomena of consciousness, super-ego and conscience, and creativity as derivatives of libido-sublimation. Existential thinking considers man as living in three spheres of existence, none of which can be derived from or explained by the others although all three are closely interwoven in the wholeness of a person: a) the world of metabolism and biological exchange, b) the sphere of emotional interaction with the contemporary living Umwelt, and c) the inner world of man—his imagery, dreams, and thoughts.

8) The difference in interpretation is of paramount importance for the procedure of psychotherapy. In presenting two cases, it is made evident that the psychoanalytical interpretation leads to a very different appraisal from that of existential analysis.

9) Existential analysis places main emphasis on the process of becoming and does not ascribe all neurotic complications to earliest childhood and the Oedipus situations. It attributes equal if not greater importance to the time of adolescence and adult development. Personality development is a process of individuation and self-realization. Thus the child develops toward an increasing self-formation, by which process the individual evolves from the symbiotic identification with his environment to his own self-realization in interpersonal interactions.

10) Existential thinking sees, as the main progress in analytical psychotherapy, that symptoms like frigidity, premature ejaculation, homosexuality and others are not pathological features rooted in the individual's deviation of libido, nor are they ego-defects, but represent abnormal responses in existential situations. Experience furnishes overwhelming evidence that all these symptoms are expressions of attitudes toward specific persons. Symptoms are never universal though they may sometimes assume fairly generalized patterns. We are not dealing with ego-defects or libido-aberrations, vested in an isolated individual, but with specific modes of interaction wherein both partners in the we-experience are of equal significance.

111 Pleasant St., Arlington 74, Mass.

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Discussion of the Papers on Existential Analysis

ROLLO MAY, PH.D.

I have the privilege of discussing three highly interesting and important papers. I propose to make some comments about the present paradoxical situation of existential psychiatry in America, and to relate some of the central ideas in these three papers to this situation.

The paradox in the attitude toward existential psychiatry lies in the fact that in this country there is a good deal of hostility toward this approach. However, if we look below the surface, we find a clear affinity between this approach and underlying aspects of American thought and character. In William James, doctor in medicine, professor of philosophy and the giant of American psychology, there is an amazing kinship with existential ideas. James shows a *passionate emphasis on immediacy of experience.* He held that you cannot know truth by sitting in a detached armchair, but only in experience which includes *willing; decision* is a necessary prerequisite to opening up of truth. A person cannot discover psychological truth about himself except as he is willing to make some decision, great or small, with respect to that truth. William James also had a great humaneness and through his own vast breadth as a man he was able to bring art and religion into his thought without sacrificing any of his scientific integrity. He practically single-handedly saved American psychology at the turn of the century from becoming lost in armchair philosophizing on the one hand or the minutiae of the physiopsychological laboratory on the other. He is in many ways our most *typical* American thinker.

James sought to understand and describe the human being in his total reality, that is as a living being, one aspect of which was the fact that the person expresses himself in action. But in the subsequent developments of pragmatism, and particularly in behaviorism in psychology, this emphasis on acting became dominant to the exclusion of the total living person. The emphasis then tended to become more and more on understanding the person solely in terms of external behavior and those aspects of experience which could be viewed from the outside, and could be measured, so it seemed, objectively and in quantifiable terms. We sought to understand and treat human personality as an object of control like the rest of nature. These developments are related, in my judgment, to modern western man's pervasive experience of isolation, alienation, and lack of identity. As Dr. Wyschogrod states: "This state of ontological uprootedness is the particular malady of modern man whose technological reason is a splendid example of the extent to which humanly constructed forms can obstruct that receptive attitude to being to which Heidegger wishes to return."

This is the point where a most significant change is now occurring in America. There is an emerging attitude which we may call "ontological hunger," shown in the questions of the meaning of human existence asked by scientists and cultural leaders of all sorts. Though I suspect that the behavioristic and positivistic emphases in American psychiatry and psychology will be dominant for some time, there are clear signs that the existential emphasis may have a profound influence as a leaven in the loaf. The existential emphasis is relatively new, of course, and open to misunderstanding as well as confusion; some of the hostility toward it is thus entirely rational.

William James also stated that every theory goes through three classic stages. First, "it is attacked as absurd; then it is admitted to be true, but obvious and insignificant; finally, it is seen to be so important that its adversaries claim that they themselves discovered it."

The existential approach in psychiatry has gone through those three stages in telescoped fashion in the last several years. Three years ago it was generally dismissed as not worth serious consideration for which the expressive word "bunk" was not infrequently used; then it was said simply not to matter; and of late the attitude has been that there is "nothing new in it—we do it all anyway."

The importance of this meeting lies in reference to this third stage. The papers this morning seem to me to point toward the distinctive characteristics of the existential approach. I want to cite three such distinctive characteristics which I see in these papers.

First, the emphasis on the fact that every method of understanding human beings is based upon some philosophical presuppositions, conscious or unconscious. The only way to keep your presuppositions from biasing your perception of, and your dealing with, human beings is to bring these presuppositions into the open and analyze them consciously. By and large our uncritically accepted presuppositions have been materialistic (as in Freudianism) or idealistic (as in Jungianism). In my judgment neither is adequate for the understanding of the living, experiencing human being. The existential approach begins with the question, What is the nature of this being, man, we seek to understand? The

presuppositions, then, are based upon the existing person. As Professor Wyschogrod brings out, Heidegger's thought has proven so cogent, powerful and fruitful to many psychiatrists and psychologists precisely because he undertakes to go below the usual presuppositions of materialism and idealism, and to find and describe presuppositions that comprehend man as the living being he is. May I remark apropos of the excellent paper on Heidegger we have heard this morning that Dr. Wyschogrod is the only person in existence, so far as I know, who has been able to make Heidegger clear.

The second distinctive characteristic of the existential approach illustrated in these papers is that the theory and therapy arise directly from this analysis of man as an existing being. This is shown in the excellent paper by Dr. Straus analyzing and describing the human situation with respect to the I-World relations. Dr. Straus begins not with some inherited theories of natural science used as a procrustean bed on which the human being is forced to lie, but rather with man as an experiencing being who exists in a pattern of relationships which we call I-World. I am always gripped by Dr. Straus' elegant work which serves, if I may say so, to put the human being back into the world again, not by fiat or faith but by a careful phenomenological and psychiatric description. I am not happy with his term, "Allon"; I wish that a term could be found that would have more of the vital reality of the "I-Thou" relationship he is talking about. But this minor caveat does not reduce my admiration for his seminal contribution.

With respect to the statement by those psychotherapists critical of existential psychiatry, "We do the same things anyway," it can be admitted that every therapist is existential in the moments when he relates authentically to the patient. But often these moments occur in spite of, rather than because of, the therapist's theory. We often hear of some moment of understanding in a therapeutic situation, some strong human interchange that grasps the patient and is crucial for the therapeutic progress, but which the therapist describes as happening "by lucky accident" or some other way not connected with his theory. The existential approach bases the therapy directly on the theory, and thus these highly therapeutic moments are not "accidents" but are logically the outcome of the theory.

This leads to the third point, namely that a distinctive characteristic of the existential approach is that normal relations rather than pathological are taken as the basis for theory. That is, the norm is not described from the pathological, but the pathological from the norm. Dr. Benda's paper gives an impressive example of this in his insistence that love cannot be understood on the basis of narcissism; he endeavors rather to understand love in terms of the norm of man's positive capacities for relating. In other words, the analysis of the neurotic forms can never tell us of *what the neurotic is a distortion.* Existential psychiatry is the endeavor to understand man's nature not on the basis of its pathology or sickness but rather on its capacities for normal functioning.

The concept of the mirror-like position of the therapist is not an adequate ground for the patinet's understanding of his I-World relationships. Certainly the patient needs to be protected from the therapist's neurotic tendencies, and even from the therapist's own subjectivity; I assume all the speakers this morning would value *objectivity* in its real sense, and specifically, objectivity in the therapeutic relationship. The point, rather, is that the only way you can be genuinely objective with a patient, that is, deal with him in terms of his own needs undistorted by your needs, and for his own best interest, is to analyze your own part in the relationship on the basis of concepts such as the I-World and sympathy. *Transference* was one of the great discoveries of Freud, to be sure, but in my judgment it cannot be understood except on the basis of understanding the nature of *sympathy.*

I value especially the emphases which point toward the implications of the existential approach for the practice of psychotherapy. I cannot agree with some of our colleagues in existential psychiatry who hold that this approach has very little if any relation to therapy. If the existential approach is true at all, it must mean that theory and therapy are inseparable, that our mere knowing of another human being involves some interrelationship with him, some participation. This person we seek to understand will always be in the process of becoming; his self, as Kierkegaard insisted, is only that which he is in the act of becoming. Psychological growth and change, as well as moral growth and change, are everpresent aspects of each individual's living experience—and to deny this only proves it from another angle. Furthermore we can find a person revealed only in critical situations: nobody will go through the agonies of baring the deepest aspects of his psychological and spiritual suffering except as he has some hope of gaining help in finding his way out of his agony. Psychiatry and psychology are two sciences which cannot know their material—i.e., persons—except as they are oriented directly or indirectly to helping these persons.

Symposium on Practical Treatment Methods

SOME EXAMPLES OF THE COMBINED USE OF PSYCHOTROPIC AGENTS
John Gibbon

PARALYSIS AGITANS SYNDROME
Alfred E. Eyres

A COMPARATIVE TRIAL OF ANTIDEPRESSANTS
George G. Haydu, Walter Brinitzer, John N. McKnight and John R. Whittier

EFFECT OF ELECTROSTIMULATION ON BRAIN 5-HYDROXYTRYPTAMINE CONCENTRATION
Carl Breitner, Albert Picchioni, Lincoln Chin and Lloyd E. Burton

A SURVEY OF SIDE-EFFECTS AND/OR TOXICITY OF NEWER PSYCHOPHARMACOLOGIC AGENTS
Reuben M. Cares and Charles Buckman

THE ANTIDEPRESSANT QUALITIES OF ELAVIL
Edwin Dunlop

ORGANIC THERAPY IN PEDIATRIC PSYCHIATRY
Lauretta Bender and Gloria Faretra

USE OF GLUCAGON IN INSULIN COMA THERAPY
H. Peter Laqueur and Harry A. La Burt

Some Examples of the Combined Use of Psychotropic Agents

JOHN GIBBON, M.D.

The last few years have seen the development of a large number of chemical agents that affect mental functioning in different ways.

It was possible ten years ago to sedate a patient to the point of coma, but thought disorders and emotional imbalances were generally unaffected, and delusional thinking would persist. The shock therapies, principally electric shock, and neurosurgery, principally bilateral prefrontal lobotomy, appeared to reduce disordered thinking, reduced anxiety and tension, and markedly lifted depression. Unfortunately, the effects of electric shock therapy are generally transient, requiring time consuming repetitive courses, disarrangement of the patient's family life, and, all too frequently, prolonged hospitalization, with its personal tragedies. Lobotomy seemed to offer hope of more permanent cure, but the sequelae, mortality rate, epileptic seizures, and personality deterioration were such that the best one can say of it is that it exchanges one type of defect for another. Insulin shock possibly offers a situation between that of electric shock and lobotomy.

The advent of chlorpromazine revolutionized the treatment of mental disorder; it catalyzed the open door policy to the point where one could envisage the feasibility of a hospital virtually completely open. About the same time, the Rauwolfia alkaloids came into use as tranquilizers. Subsequent experience has indicated that while these alkaloids tranquilize the patient in the sense that he is calmer, without being necessarily drowsy, there is a qualitative difference between them and the phenothiazine derivatives. The more potent of the latter may or may not produce calming in the ordinary sense, but will change the character of disordered thinking, reducing delusional content, and often abolishing hallucinations. There is greater reality testing, and affect is often more appropriate, even though it may have a wooden or restricted quality to it, characteristic of the chronic schizophrenic reaction.

An example of this qualitative change in thinking is given by a lady in her 60's, who was previously receiving promazine. She had the delusion, in which she was quite happy, that the physician then in charge of the service in which she resided was her husband. She was later given chlorpromazine, but the delusions, though perhaps a little less florid, remained essentially unchanged. When a combination of mepazine with chlorpromazine was given, the delusions changed radically; the physician became a good friend; he was no longer her husband. Coincidentally, her affect, previously neutral or a little elated, became a little more depressed, and its range remained limited. However, her previous physician was a handsome man, and since we had dissolved her marriage chemically, perhaps she had reason to feel depressed. In Freudian terms, the anger associated with her object loss had been turned against herself; it might well have been turned against us too, as perpetrators. She developed some tremor on phenothiazine therapy, but no sedation, or even tranquilization in the mere sense of the calming of anxiety or agitation seen with the use of Rauwolfia alkaloids, the meprobamates, and some other tranquilizers.

Thus two kinds of tranquilization appear to be involved, both different from the earlier sedative and hypnotic effects. There are (1) sedatives—barbiturates, anesthetic agents in general; (2) tranquilizers — Rauwolfia alkaloids, meprobamates, hydroxyzine; (3) euphrenics—phenothiazines, of three main categories; those with an aliphatic tail in the 10th position on the phenothiazine nucleus, those with a piperidine tail, and those with a piperazine tail. The word euphrenic is used to imply well thinking, or increased reality testing with loss of distortion. Of course, it may be objected that there is often overlap in these three; Rauwolfia sometimes reduces disordered thinking; phenothiazines sometimes sedate; sleep therapy has been used with the idea that prolonged narcosis would allow restitution of normal mental functioning. But the broad distinction still remains, and it is now generally possible to produce sedation, going on to drowsiness and sleep with the first group, tranquility or calmness without change in disordered thought processes and without drowsiness of any marked degree with the second group, and euphrenia, or good reality testing with reduction in disordered thought processes with the third group.

A fourth group of compounds should be mentioned here, since it plays an important part in

From Creedmoor State Hospital, Queens Village, New York.

the concept of combined therapy: (4) energizers, or anti-depressants—Tofranil, Nardil, Niamid, Marsilid, Marplan, Benzedrine—these generally relieve both the depression and the psychomotor retardation; appetite may be stimulated, as with Marsilid, or depressed, as with Benzedrine.

Within the third group of compounds, the phenothiazines, the division into three subgroups is important, not only because of chemical structure, but also on a clinical basis. Those with an aliphatic tail tend to have sedative effects (for example, chlorpromazine); those with a piperidine tail tend to be without significant sedative or stimulant effects (for example, mepazine); those with a piperazine tail tend to have stimulant effects (for example, prochlorperazine and fluphenazine). All three have this normalizing effect on thought processes.

These comments apply to the usual effects of phrenotropic compounds, but in practice each patient may show a wide range of responses to each compound; in some, a particular compound may prove highly effective, as if tailored to their individual needs, and toxic effects may be minimal or absent; in others, little or no improvement may be observed before toxic or allergic signs appear. A number, however, will show improvement with one compound, but, even in the face of high doses, fail to show good remission of delusional thinking. It is therefore obvious that some psychotic patients will respond well to one tranquilizer, and may be released from the hospital to continue taking the drug. Others will fail to reach this degree of improvement on one drug alone.

There are many examples in medicine of the successful combined use of similar drugs to potentiate effect without increasing toxicity; the familiar A.P.C. tablet and its many homologues is a good example; triple sulfonamide is another. Pushing dosages of individual drugs to high levels, with corresponding increases in side effects has several disadvantages: first, you must treat the side effects; secondly, high dosages often don't work; thirdly, the emotional reactions of the patient may not be suited by one drug alone; there may be depressive features, calling for mood elevating therapy with a drug of the energizer group; persistent delusional trends may call for a drug of the euphrenic group, and the choice here may be varied according to whether sedative effects are needed in addition, whether normalizing only is needed, or whether stimulant effects are needed. Delusional trends may be controlled with one or two euphrenics, but overactive, or aggressive symptoms of anger may still persist. In such cases the simple tranquilizers, such as a drug of the reserpine series, or hydroxyzine, may supply the missing link in the therapeutic chain, which brings the patient back to a point where he may begin to accept normally regulated social functioning. In these cases, a sedative, such as Phenobarbital, may also often be useful in reducing gross overactivity.

A further important consideration in the combined use of two tranquilizers is that side effects may not only fail to be increased, but, in some combinations, may actually be decreased by the combination. It is to be noted in this connection that some agents used in the treatment of the side effects of phenothiazines, such as parkinsonism, are chemically closely related to the phenothiazines. The antagonism of two such compounds in regard to toxic effects may be related to their mutual competition in intracellular microchemical reactions while their therapeutic effects are additive. One such clinically highly effective combination is chlorpromazine (Thorazine), with mepazine (Pacatal); the latter was introduced as an agent to control the toxic effects of phenothiazine, but is itself a potent member of the "middle" group of phenothiazines, having a piperidine tail, and normalizing phrenotropic qualities. Thus a powerful anti-delusional effect is produced with a diminution in side effects. The sedative qualities of this combination can be increased or decreased as the amount and relative proportion of Thorazine in the combination is increased or decreased. Reactions to Pacatal, such as blurring of vision and dryness of the mouth, call for a reduction in dosage. It is a remarkable fact that, generally, the more severely psychotic patient will tolerate larger doses of phenothiazines without toxic symptoms, while often times the neurotic patients, and normal individuals may complain of the side effects of Thorazine and Pacatal even in low doses. One might almost be tempted to suggest a diagnostic test along these lines. These remarks do not apply to all phenothiazines. For example, prochlorperazine (Compazine), is well tolerated in ordinary dosage by most normal individuals, but interestingly enough, has a lower euphrenic index than Thorazine and Pacatal.

Another group of patients treated have been those with epilepsy, usually of grand mal type, in whom the phenothiazines have been suspect as triggering agents of convulsive seizures. If one takes into account one theory of their mode of action, that is, that they set off local discharges in neurones concerned with the feed back

mechanism between the cortex and the hypothalamus, thereby putting these neurones temporarily out of action and reducing the affect of anxiety and its concomitants, one can see that even though fairly selective, this effect may spread in some minor degree to other neurones, including those of the cortex. In line with this theory of phenothiazine action, one sees no sudden reversion when they are withheld in a psychotic person whose symptoms have been controlled by them. Often there is a period of well-being, followed by gradually increasing tensions, as the feed back mechanism begins to take its effect. Only later is re-development of the secondary symptoms of delusions and hallucinations seen. Generally, too, the epileptic patient will tend to have episodes of irritability, assaultiveness, selfish and demanding attitudes, rather than the more florid distortions of the schizophrenic. Sometimes, a co-existence may occur, but more commonly, the epileptic who is also considered psychotic, shows the first mentioned picture. This will usually respond to treatment with the simple tranquilizers and sedatives. Hydroxyzine (Atarax or Vistaril) has proved very useful in this regard, since it apparently has no tendency to trigger convulsions, is virtually free of toxic side effects, and is an effective, simple tranquilizer. It is well received by patients, who say they feel clear and mentally alert when on it, as compared with the phenothiazines, with a considerable diminution in irritability. Such a drug is, of course, used in combination with anti-convulsants, such as Dilantin, Mysoline, and Phenobarbital; the latter is useful in a dual respect, in that it also dampens aggressive activity. However, in some cases, epileptic patients who show more severe psychotic symptoms have been given phenothiazines with increased anti-convulsant coverage, and have shown good responses, and without significant increase in seizures. Apparently, whatever convulsant effect the phenothiazines possess can be controlled in this way.

Clinical

The patients in this survey were drawn from a continued treatment building of about 700 census, with assorted psychiatric and neurologic disorders. The survey was made October 18, 1960.

Records were available on 60 patients put into process for release between February 1 and June 1, 1960; another 37 were processed, but their records were not available for analysis for various reasons. The release process included an interview of the patient and of the family by the psychiatrist, a social service investigation, and final interview and decision by the release officer. This process took about a month. It so happened that of this group of 60 exactly half were released on one medication only, and the other 30 were receiving combined drug therapy. The scatter throughout the four month survey period was about even. Of the 30 patients receiving one medication, five had returned to the hospital from convalescence, whereas of the 30 receiving combined therapy, none had returned. Now, these figures are too small for reliable conclusions, and over a longer period of time, I'm sure the figures would not be so unilateral. However, they are selective only in that they include those on whom data are available to me, and who have been on convalescence for three months or so. I should add that I have no way of knowing whether these patients continued to take the medications I prescribed, or which they were taking when they left the hospital, since at that point they became the patients of the psychiatrist in the Aftercare Clinic in the borough in which they resided. However, I tried to emphasize to the patients about to be released, the importance of their continuing to take the medication or combination of medications which had aided their improvement. To break down the figures somewhat, of those released on one medication, 15 received Thorazine, 6 Compazine, 4 Trilafon, 2 Sparine, 1 Vesprin, 1 Equanil and 1 Nardil. Of those released on combined therapy, ten received Thorazine and Tofranil, 5 Thorazine and Pacatal, 3 Sparine and Tofranil, 2 Thorazine and Phenobarbital, 1 Compazine and Stelazine, 1 Trilafon and Tofranil, 1 Compazine and Tofranil, 1 Thorazine and Compazine, 1 Thorazine and Sparine, 1 Thorazine and Serpasil, 1 Thorazine and Nardil, 1 Sparine, Pacatal and Tofranil, 1 Thorazine, Pacatal and Nardil and 1 Vistaril, Tofranil and Phenergan. Of those on one medication who returned, 2 received Thorazine, 1 Trilafon, 1 Compazine, and 1 Equanil.

However, what has been more gratifying at the clinical level than the counting of numbers, has been the evident improvement in the mental condition of many patients through the use of such combined therapy methods, devised on a purely empirical basis. Even those patients who have not as yet reached a point where they have been recommended for release, have shown considerable improvement in mental status, have become more friendly, cooperative, and interested in their surroundings, with diminished delusional activity. Families would see improvement after years of hospitalization, often with failure to respond to one medication alone. The follow-

ing case summaries illustrate in a little more detail the use of combined therapy.

M.M. is a 34-year-old woman who was admitted to the hospital in January of 1955, and diagnosed as schizophrenia, mixed type. At that time, she showed evidence of a thought disorder, spoke of her deceased father visiting her, would alternately laugh and cry, and exhibited hyperactive behavior, with speech under pressure, that was rambling, irrelevant, and with religious preoccupation. She was released several times on convalescent status, with stays of several months at a time, and she was away once for four months on elopement. Each time she returned with a recurrent thought disorder. Electric shock treatment would lead to a brief period of improvement only. She was given Thorazine 100 mg. three times a day with considerable improvement, but remained a little moody, and, at times, moderately depressed. Tofranil 25 mg. three times a day was added, and considerable further improvement was noted; she made a good impression, was attractively and tastefully attired, was normally spontaneous, gave relevant responses, recognized that she broke down, with the former delusions of her family placing her under hypnosis. Her affect was appropriate and there were no evident abnormal trends. The psychiatrist who is our release officer assessed her as employable without limitations, and she was released on convalescence.

E.B. is a 60-year-old woman who was admitted to the hospital 16 years ago on a regular order of certification, and diagnosed as paranoid schizophrenia. Seven years prior to her admission, that is, 23 years ago, at the age of 37, she began to say that the devil put bad thoughts in her mind; she became seclusive, suspicious, irritable, and overly religious, entering stores to preach to the people to convert them to religion. The family could no longer care for her, and they took her to Bellevue Hospital Observation Ward; there, she was restless, overtalkative, and misidentified people, and was transferred to this hospital. She received 14 electric shock treatments from January to April of 1945, but showed little improvement. She believed her people kept her hospitalized unjustly, and periodically was noisy, overtalkative, and hypochondriacal. In September of 1958, she was receiving Sparine 50 mg. twice a day, to which Thorazine 100 mg. twice a day was added in October of 1959. Dosages were increased to 200 mg. three times a day of Thorazine, and 100 mg. three times a day of Sparine by February of 1960, without considerable improvement. She was placed on Pacatal 100 mg. three times a day, Sparine 100 mg. three times a day, and Pyribenzamine 50 mg. three times a day in February, and thereafter she showed steady improvement. Because of blurring of vision, Pacatal was reduced to 100 mg. once a day in June, but her improvement continued. Her family took her home on weekends from March of 1960, and these were described as satisfactory; she became friendly, well behaved, industrious, enjoyed needlework, helped with the housekeeping, and showed no evidence of delusional beliefs or hallucinations. However, she could give no reasons for her hospitalization, stating only that she was run over by a car. Her husband requested her release; she went home on convalescence, the first time in 16 years.

A word on the addition of antihistamines, such as Phenergan and Pyribenzamine, to combined therapy may be in order; the original work on phenothiazines, promazine and chlorpromazine, in France, included the use of Phenergan in combination with these agents, and the combined therapies above described are therefore, in a way, only the off-shoot of this French contribution. I have tended to use antihistamines rather where some allergic symptoms appeared; these allergic symptoms sometimes have been present prior to tranquilizing therapy, and have not necessarily been increased by it, but, in the face of an allergy, tranquilizers are often discontinued by physicians. It is in such cases that continued, combined use of an antihistamine with the other medications has usually been recommended.

V.M. is a 46-year-old woman who was admitted to Harlem Valley State Hospital in March of 1956 with depression, fears that she might harm her children, and auditory and visual hallucinations; in a previous admission to Bellevue Hospital in April of 1953, she was described as a helpless, inadequate, and dependent person with a low energy level. At Harlem Valley, she was evasive, illogical, panicy and suspicious. She was given Thorazine for two weeks, but this was discontinued because of jaundice, and her mental condition remained unchanged. A course of 17 electric shock treatments resulted in her being essentially the same as at the time of her admission. She was diagnosed as schizophrenia, mixed type. In March of 1959, she was still described as apathetic and idle; she made somatic complaints, and was emotionally extremely flat and inappropriate. On August 2, 1960, she was transferred to this hospital, where the same symptoms were noted as above. She was given Stelazine 5 mg. twice a day, and subsequently 15 mg. once a day, and became more spontaneous, although her affect remained dull; her speech was relevant but circumstantial, and delusions and hallucinations were not elicited. She was then given, in addition, Tofranil 50 mg. three times a day. Her spontaneity, attention, and interest appeared to improve; she became cooperative, well behaved, helped with the ward routine, and had an honor card and weekend privileges, which were described as being satisfactory. She took an interest in her appearance, but showed little or no insight, and could not remember the events which led to her hospitalization. Her mother requested her release on convalescence, and this

was approved. Although far from well, she had shown considerable symptomatic improvement.

B.M. was a 46-year-old woman with a history of epilepsy since infancy, at first petit mal, but now grand mal, with a frequency of about one seizure every two months, worsened in some degree by her previous excessive beer drinking. She showed some bizarre thinking with loosening of associations, mild euphoria, and somewhat inappropriate affect; her sensorium was clear and insight was defective. She was diagnosed psychosis due to convulsive disorder, epileptic deterioration. She was given Dilantin and Phenobarbital for the convulsive disorder, latterly 1 capsule, 1½ grains, of Dilantin daily and 1 grain of Phenobarbital daily. Though at first given phenothiazines, she showed little improvement as far as her weekends at home were concerned. Her husband was concerned because she would throw out his clothing; in other respects, her thinking did show signs of improvement. Because of this, and because she experienced feelings of depression, she was placed on Vistaril 100 mg. three times a day and Nardil 15 mg. three times a day, in addition to the Dilantin and Phenobarbital. She became friendly, alert, and normally spontaneous. In the ward she worked regularly in the sewing room; at home, her relationship with her family improved considerably. On interview, she appeared neatly dressed, and younger than her chronological age; evidence of organic deterioration was minimal, and she had had no seizures since admission to the hospital. She said she did not understand why she felt compelled to do "foolish things." Her affect was appropriate to her ideation, and no abnormal trends were found. Her husband requested her release, and this was approved on October 20, 1960.

Paralysis Agitans Syndrome:

A Report of the Results of Testing and Treatment with High Frequency (Sedac) Currents

ALFRED E. EYRES, M.D.

The high frequency (sedac) currents used in this treatment project have been defined and elaborated in an earlier presentation.[1] Briefly, the instrumentation utilized in production of the high frequency (sedac) currents is the Reiter S.O.S. Electrostimulator. This instrument delivers in the testing and treatment situation variable bursts of current reaching to 1,000,000 cycles and more. Power may be varied from a fraction of one sedac unit to 1,500 units. The sedac unit is a descriptive electronic term and serves as a substitute equivalent for highly complex mathematical formulation of many frequencies at various intensities. The principle followed in formulating the sedac unit is similar to that used in defining the Roentgen unit as the complex formulation of an x-ray beam.

In sharp contrast to galvanic current, the sedac currents are capable of stimulating both sensory and motor components throughout a wide range, yet remaining well under the pain discomfort threshold.

High frequency currents were introduced into medicine about five years ago and appear to have opened an entire new field for investigation. A number of investigators have published papers dealing with this subject.[2-15] Clinicians report effectivity of therapy in functional disorder, in organic psychiatric syndrome and in neurological entity.

Two years ago two male patients with Parkinson's disease, sustained psychotic disorder and were admitted to the Psychiatric Service of the Jennings Memorial Hospital. They were placed on high frequency therapy, each receiving four hours of treatment weekly over a period of four weeks. Not only did the psychotic situation lessen in intensity but the neurological symptoms also were relieved. Viewing these results it was thought that it might be interesting and rewarding to test and treat a pilot series of paralysis agitans cases of as pure a neurological culture as possible.

A discussion of theory, mechanism, action and techniques have been described and published previously.[1] A short explanation, however, is in order. As in other types of electrocerebral therapy, the specific action of high frequency current in the therapeutic procedure is unknown. The high frequency testing procedures are based upon the principle of "excitation." The minimum sensitivity and the maximum tolerance modalities constitute the extremes of the excitation factor. The first modality is defined as the sedac unit value noted when the patient first perceives the current. The second modality is the value noted at the upper limit of the pain discomfort threshold.

Sedac testing and treatment is instigated over many "brain areas" by varying the position of the scalp leads. A single brain area may be tested or several areas may be enveloped, tested and treated together. The positive and negative lead sets of wires emerging from the instrument may be made fast to the subject in either of two ways. If one electrode is secured to an extremity (usually the right forearm) and the other is placed on a specific scalp area, the method is designated as monopolar. If both positive and negative electrodes are fastened to specific scalp areas, the method is described as bipolar.

The several "brain areas" may test and treat within the normal range, ultra sensitive range or the more insensitive range of current intensity. An approximation of the "normal" and abnormal sedac unit values, the result of five years of investigation, has been determined and described.[11,14]

This paralysis agitans treatment project was sponsored and assisted in part by a grant-in-aid from the Grace Hospital, Detroit, and was conducted during the summer of 1959 at that institution. There were 11 patients in the project referred by private physicians. Four were females and seven were males. Etiological factors varied widely and duration of illness likewise was diverse, varying from five to 20 years with a mean average of 8.7 years.

A total of 270 biweekly treatments were given, and the duration of each treatment varied from 50 to 90 minutes. Each patient was sedac tested for minimum sensitivities and maximum tolerances initially, midway through therapy and at termination. In addition, each was given a neurological examination and an electroencephalogram.

Table I describes pertinent data concerning each patient. Figures 1 to 3 are logarithmic

graphic presentations of five patients. Each graph portrays the minimum sensitivities and the maximum tolerances initially, after 12 treatments and at termination. Vertically and to the left are designated the sedac unit values. Below and horizontally, the legend defines the test-treatment positions and data.

All patients were treated with different leads, some with monopolar and others with bipolar. This differentiation was determined largely by two factors. The first was based on the abnormal test values of any given area. For example, if the left temporal area and the right occiput area measured abnormal, the two areas were enveloped and treated. On the contrary, if the right parietal area and the vertex anterior area measured within the range of normal, treatment was not applied to these areas. The second factor dealt with comfort and tolerance of treatment proper. If the patient tolerated therapy and progressed more satisfactorily with monopolar rather than bipolar leads (or vice versa) his therapy was given accordingly.

If properly and skillfully given, patients have

TABLE I

High Frequency (Sedac) Testing and Treatment of Eleven Cases of Parkinson's Disease

No., Case and Yrs. of Illness Age, Sex and Marital Status	Etiology	Medication During Therapy	Sedac Test Findings	E.E.G. Findings	Symptoms, Findings, Impairment
1. M.H. 7 66—F Mrd.	Art. Scl.	Artane Benedryl	All areas reduced maximum tolerance and dulled minimum sensitivity.	Dysrhythmia Grade (1) Generalized	4 plus gait, station, rigidity, tremor, movements, vasomotor, pain in left arm.
2. P.P. 10 71—M Mrd.	Art. Scl.	None	All areas elevated maximum tolerance.	Normal	1-2 plus facies, gait, station, tremor, and movements.
3. A.S. 6 59—F Mrd.	Art. Scl.	None	Occiput and vertex posterior areas elevated maximum tolerance.	Dysrhythmia Grade (2) Left Temporal	1-2 plus gait, station, rigidity, movements, head tremor.
4. L.V. 5 61—F Mrd.	Trauma (Head Injury)	Hyocine Benzedrine Barbital	Occiput and jaw areas elevated maximum tolerance.	Dysrhythmia Grade (2) Generalized	4 plus fatigue, facies, gait, station, movements, tremor, rigidity, pain extremities, depression.
5. A.D. 10 65—M Mrd.	Virus Infec. Shingles	Artane	All areas elevated maximum tolerance and ultra minimum sensitivity.	Dysrhythmia Grade (2) Generalized Bitemporal	3-4 plus fatigue, facies, gait, station, rigidity, tremor, vasomotor, oculogyric and depression.
6. T.P. 11 75—M Mrd.	Previous Encephalitis (1918)	Artane	All areas elevated maximum tolerance.	Normal	3 plus fatigue, facies, gait, station, rigidity, tremor, movements, speech, oculogyric.
7. S.H. 6 79—M Mrd.	Art. Scl.	Hyocine	All areas elevated maximum tolerance.	Dysrhythmia Grade (1) Bitemporal	4 plus facies, gait, station, rigidity, tremor, movements, vasomotor, speech.
8. P.P. 7 67—M Mrd.	Art. Scl.	Hyocine Benedryl	All areas elevated maximum tolerance.	Dysrhythmia Grade (2) Bitemporal	3-4 plus gait, station, rigidity, movements, vasomotor, depression.
9. F.M. 7 70—F Mrd.	Art. Scl.	Barbital	All areas elevated maximum tolerance and dulled min. sens.	Dysrhythmia Grade (2) Generalized	3-4 plus fatigue, gait, station, rigidity, tremor, movements, oculo-gyric.
10. W.V. 7 75—M Div.	Art. Scl.	None	All areas elevated max. tol. and ultra min. sensitivities.	Dysrhythmia Grade (1) Generalized Max. L. temp.	2 plus tremor hands, rigidity, movements.
11. H.W. 20 59—M Mrd.	Encephalitis Following Smallpox	Artane Benedryl	All areas elevated max. tol. and dulled min. sens.	Dysrhythmia Grade (1) Generalized	4 plus fatigue, facies, gait, station, rigidity, tremor, movements, pain extrem.

no fear of sedac therapy. Actually, the therapy gives comfort. The term sedac is used because the high frequency currents possess sedative-like qualities. Most of the patients fell soundly asleep during the entire therapy interval.

The criteria of improvement resulting from therapy was based upon the observations and evaluations of the author, consultations with relatives or friends of the patient and the statements of the patients themselves. The phenomena of transference was carefully considered and was not discounted.

Of the 11 patients treated, nine were substantially improved, one was slightly improved and one unimproved. The improvement in each situation consists of the following:

Case No. 1: Lessened fatigue; elevated spirits; increased general activity; locomotion improved; ability to tie shoe laces increased.

Case No. 2: Generally improved in all spheres; more active; spirits elevated.

Case No. 3: Generally improved; lessening of spasm and tremor of head and neck muscles.

Case No. 4: Locomotion, general movement and speech improved; tremor lessened; spirits improved; extremity pains relieved.

Case No. 5: Elevated spirits; increased mental clarity; five movements improved; patient does odd jobs about house and yard, the first he has done in two years.

Case No. 6: Locomotion improved; facial tremor lessened.

Case No. 7: Unimproved.

Case No. 8: Unimproved except for better spirits.

Case No. 9: Spirits improved; mental clarity increased; somewhat more active in household work.

Case No. 10: Tremor is much improved; he han-

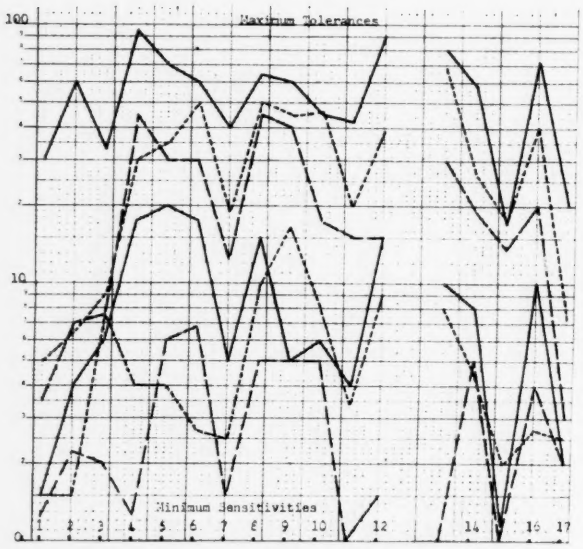

Figure 1. Paralysis agitans syndrome: Case No. 1. High freq. (Sedac) testing and treatment.

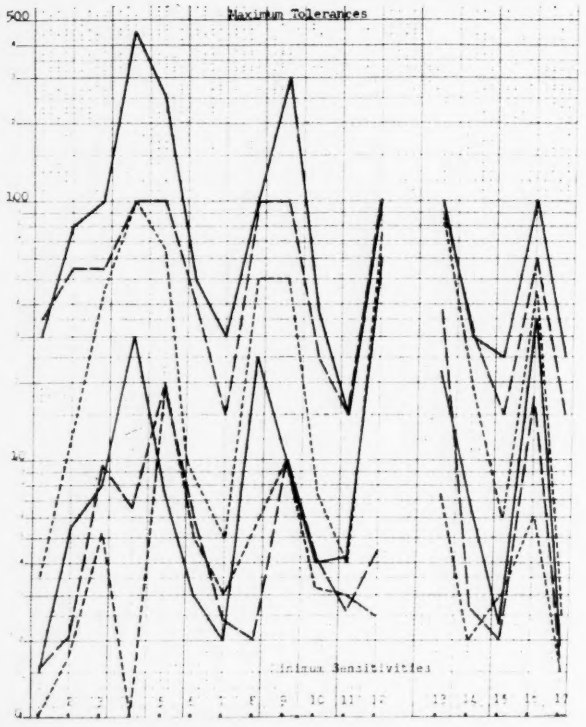

Figure 2. Paralysis agitans syndrome: Case No. 4. High freq. (Sedac) testing and treatment.

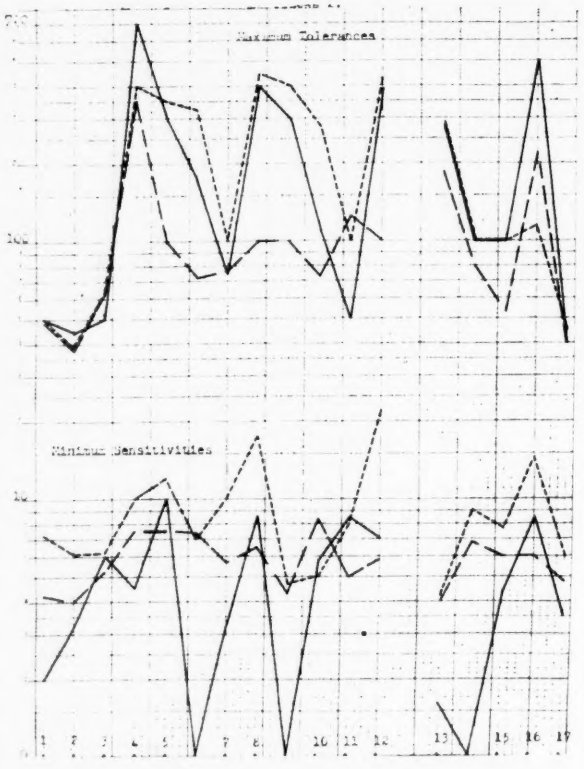

Figure 3. Paralysis agitans syndrome: Case No. 10. High freq. (Sedac) testing and treatment.

dles cup, glass and toothbrush better; mental clarity and spirits are up; he is more relaxed and less rigid, walks more easily.

Case No. 11: Much improved; has had no falls; spirits and mental clarity are elevated; drooling less; locomotion improved; working on lawn and pulling weeds which he has not done for three years.

The instigation of effective therapy in any organic brain syndrome, whether psychiatric, neurologic or both, is a formidable undertaking. Not only is any therapy frequently discouraging, it becomes perplexing as the disease process progresses.

All subjects treated had sustained long-standing deeply ingrained illnesses. At the onset of therapy, effort was made to reduce or discontinue all drug medications. In our 11 patients, we were successful in removing three from medication while the electrocerebral therapy was in progress. Parkinson's disease patients are sometimes described as a rather "pill-happy lot." Indeed, they are quite uncomfortable and accustomed to high medication intake. During the summer of 1959, Detroit in particular and the country in general, experienced an extremely hot and humid summer. Frequently, telephone calls were received from the patients asking to resume medication for this reason alone. This may have been a valid reason.

It is concluded that, as in certain other chronic brain syndrome disease, the high frequency currents may come to have a place in treatment of paralysis agitans. It is further concluded that, while treatment perhaps need be neither more intense nor more frequent, it should be carried out over a much longer time interval. Because of many exigencies, this project had to be limited in scope.

17800 East Eight Mile Rd., Detroit 36, Michigan.

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A Comparative Trial of Antidepressants

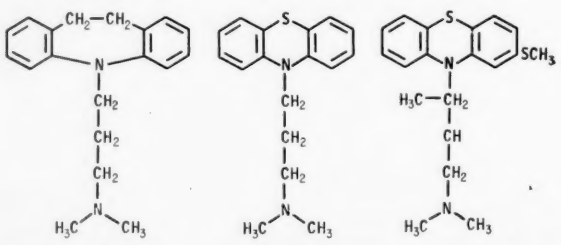
GEORGE G. HAYDU, M.D., WALTER BRINITZER, M.D., JOHN N. MCKNIGHT, M.D., and JOHN R. WHITTIER, M.D.

Five drugs for the treatment of depression reached the pharmaceutical market during the months of July and August of 1959. They quickly competed in the psychiatrist's therapeutic armamentarium for the treatment of this syndrome. The simultaneity of appearance and the equal claims for superiority suggested the need for comparative evaluation. Such a study was organized in the fall of 1959 and provides this preliminary report of our findings on a population of over 100 patients. Subjects selected were of both sexes, in ages ranging from 27 to 77 and recently hospitalized. They entered the study population in random enrollment as admitted to Creedmoor State Hospital and were selected by the supervising psychiatrists. The principles of selection concerned the syndrome of psychotic depression and not the different clinical diagnostic categories. Although the most frequent psychiatric diagnoses encountered were involutional melancholia and schizophrenic reactions, the patients were selected solely on the basis of the syndrome depression. This syndrome was divided into three symptom groups on our report forms:

1. Symptoms related to self concept such as hopelessness, worthlessness, personal neglect, guilt, suicidal ideation and suicidal activity.
2. Physiological symptoms, such as fatigue, underactivity, agitation, insomnia, weight loss, etc.
3. Related symptomatology, such as aversions, somatic delusions, and ruminations.

Patients were started on treatment with either imipramine (Tofranil), or one of the following drugs: phenelzine (Nardil), nialamide (Niamid), isocarboxazid (Marplan) or JB-516 (Catron). The following dosage schedule was adopted: Tofranil—50 mg. t.i.d., Nardil—45 mg. o.d., Niamid—150 mg. o.d., Marplan—30 mg. o.d., Catron—18 mg. o.d. All drugs used in this study, with the exception of Tofranil, are known as inhibitors of amine oxidases: they have the ability to inhibit the enzyme activity that destroys amine substances such as nor-adrenalin and serotonin, which have been found to constitute essential neurohormones in the transmission of nervous impulses, particularly in the hypothalamus and selected subcortical portions of the brain.[1,2]

From Creedmoor State Hospital, Creedmoor Institute for Psychobiologic Studies.



Figures 1 and 2.

Tofranil on the other hand, has negligible action as an amine oxidase inhibitor. It is closely related in chemical structure to promazine (Fig. 1). Tofranil has a CH2-CH2 group instead of a sulphur atom connecting the two benzyl moieties of the phenothiazine configuration. This quality produces a lack of coplanarity of the two cyclic structures (Fig. 3). Another phenothiazine preparation, the SKF 6270 was also reported to have a significant antidepressant effect.[3] The structural formula of this substance is also very close to promazine (Fig. 2). Here, too, as in the case of Tofranil, the methyl group at the 2-propyl position with the thiomethyl group in the phenothiazine ring produces a noncoplanarity. Tofranil has a distinct physiological effect on structures which respond to monoamines. For example, Tofranil markedly increases the vasopressor effect of nor-adrenalin and increases the sensitivity of the nictitating membrane of the cat to serotonin, which chlorpromazine is not capable of doing.[4,5]

MOLECULAR MODEL OF PROMAZINE AND IMIPRAMINE

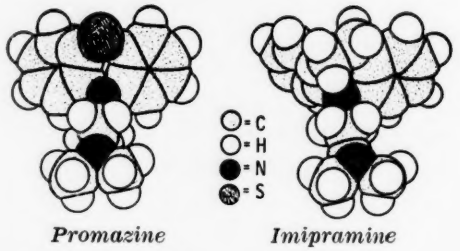


Figure 3.

The drugs were used for four weeks or longer. If during the period an amine oxidase inhibitor did not produce substantial improvement, it was replaced by Tofranil. In the case that Tofranil was the first drug administered and proved to be

ineffective, one of the amine oxidase inhibitors was substituted after four weeks. If the depression appeared refractory or dangerous to the patient, electroshock therapy was given. The results were evaluated by the attending psychiatrists and recorded biweekly on a special form. Improvement was judged as "marked" or "moderate" and referred only to the psychotic depressive syndromes.

Preliminary results with three drugs are shown in Figure 4. Results for Marplan and Catron are not shown because the number was not sufficient. Catron has, meanwhile, been withdrawn from the market. "Marked" and "moderate" improvement and "no improvement" were calculated as per cent figures of the total population on that particular drug. The figures indicate, that the best results were obtained with Tofranil and the next best with Nardil. This appears to agree with the recently published[3] results of Freyhan (Fig. 5). However, in this series, we did not see the marked difference in therapeutic efficacy between Tofranil and the amine oxidase inhibitors reported by Freyhan. The improvement from Tofranil in our population was 73%, which concurs with Freyhan's figures, but he found Niamid practically ineffective and recorded Nardil failure as 50%. The improvement for Nardil in our population was 70% and for Niamid 66%.

Toxic reactions or side effects including postural hypotension, blurred vision, loss of libido, dry mouth, did not influence discontinuation of the drugs. Whenever the antidepressant drugs had to be terminated, it was for the lack of therapeutic effectiveness. No significant difference of antidepressant effect by clinical diagnosis was found. All forms of depression syndrome appeared to be helped. Age did not seem to bring any difference, unlike the reports of Freyhan. Of course, the patients in this study constituted a different population by virtue of different principles of selection, and clinical judgment was restricted in this study only to the feature of the depressive syndrome.

IMPROVEMENT OF PATIENTS AT C.S.H. IN PER CENT OF TOTAL NUMBER ON EACH ANTIDEPRESSANT DRUG

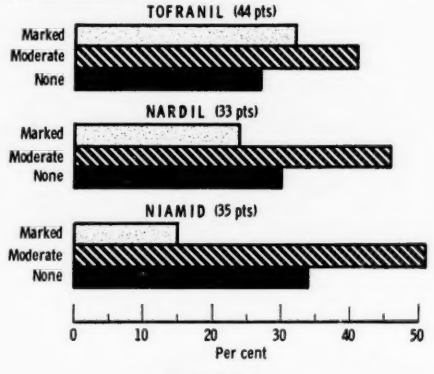


Figure 4.

CLINICAL EFFECTIVENESS OF ANTI-DEPRESSANT DRUGS (BY FREYHAN)

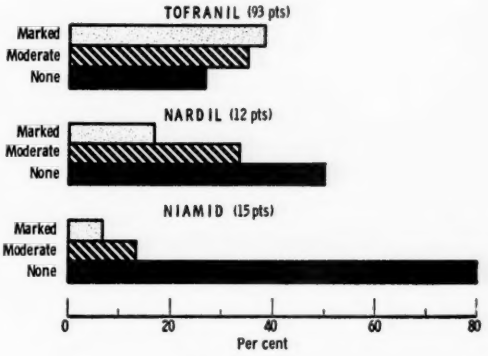


Figure 5.

Some comments are indicated on a theory of depression which contributed to our observational method. Depression may be conceived not so much as an outcome of guilt or self-blame, as described in the past, but rather as the behavioral and conceptual manifestation of marked diminution of ego cathexis.[7] Guilt used to be a more paramount secondary development, what Hoch called[8] secondary elaborations. But cultural evolutionary changes favor other elaborations in our times. Nowadays we do not blame ourselves as easily for the feeling of worthlessness as in the immediate post-Victorian period. It appears that in the syndrome of depression the drives of the organism find no integrated fulfillment through the patient's ego structure. This is not for the fact that such forces are lacking. For studies on adrenocortical functions in depression[9] blood pressure, muscle tone, and graphic signs[10] seem to indicate that a depressed patient is not an enfeebled, exhausted, listless, effortless system. On the contrary, large unfulfilled and uncathected forces are pent up which find the past habitual ways of the ego structure useless, worthless, and often move to annihilate them.

The depression symptomatology alone gives no information whether the ego structure itself is intact, the way it usually is in simple depression; or whether it is dissociated, the way it is in schizophrenic depression; or whether it is focally unintegrated, the way it is in severe obsessive-compulsive depressions. We find that the syn-

USE RATES FOR THREE ANTIDEPRESSANT DRUGS

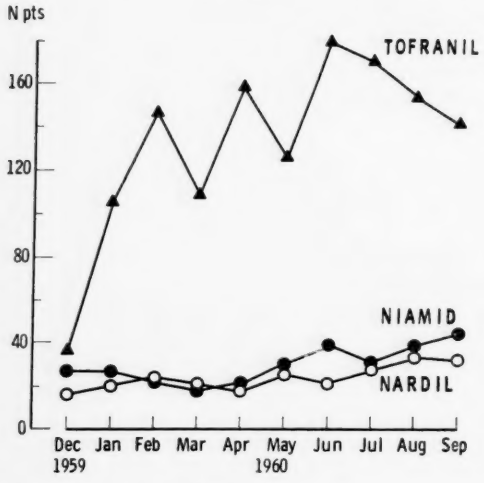


Figure 6.

drome of psychotic depression is often ameliorated by drugs regardless of the functional status of the self-structure itself.

It was observed that the psychotic depressive syndrome can be successfully lifted in the majority of cases. It is here where clinical caution and good psychiatric sense must be used. For the recathecting of the self-structure does not mean an improved or a more integrated ego. If it was a schizophrenic dissociated system, it will stay as such even after the depression has gone. If it was an unsatisfactory, unfulfilling pattern of needs kept in place only by some rigid external commandments, it will stay as such even after the simple depression has been lifted. The sequestration of the obsessive complex will still be present after the depression. Even the work of mourning[11] cannot be undone by drugs. But at least the opportunity is granted for a possible resolution.

Our preliminary findings may be compared with use-rates for antidepressant drugs, as obtained from Report of Special Therapies forms, presented in graphic manner (Fig. 6). The figures cover all patients under treatment, including those on services other than the Admitting Service on which our study is being conducted. Since the survival of the fittest drug is often a measure of its effectiveness,[6] drug use-rate to date appears to confirm our findings of comparative effectiveness.

We wish to emphasize that psychotherapeutic measures are not supplanted by drug therapy. In fact, when the drives reflood the configurational self-structure, there develops a certain newness of it, a certain rekindled zest even if this will not result necessarily in a hypomanic state. At this time the patient is amenable to therapy and all the more because his recovery was due to medical intervention. We will not fulfill his trust if we cannot provide at this point adequate psychotherapy—regardless of which drug may, by such comparative experiences as those reported here, recommend itself for use.

George G. Haydu, Associate Research Scientist (Psychiatry), Creedmoor Institute of Psychobiologic Studies.

Walter Brinitzer and John N. McKnight, Supervising Psychiatrists, Creedmoor State Hospital.

John R. Whittier, Director of Psychiatric Research, Creedmoor Institute for Psychobiologic Studies.

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Effect of Electrostimulation on Brain 5-Hydroxytryptamine Concentration

CARL BREITNER, M.D., ALBERT PICCHIONI, PH.D., LINCOLN CHIN, PH.D., and LLOYD E. BURTON, M.S.

The mode of action of electrotherapy in psychiatry is unknown, although electroshock treatment has been in use for over 20 years. It is suggested that the mechanism of therapeutic action may involve an alteration of neurohormone levels in the brain. This postulation is based on two facts: (1) certain mental disorders, particularly depressions, respond favorably to both electrotherapy and drug therapy, (2) drug therapy in mental depressions involves primarily the use of amine oxidase inhibitors, which have the ability to increase the neurohormones norepinephrine and 5-hydroxytryptamine (5-HT) in the brain.[1,2] In view of these relationships, it is believed that the beneficial effect of electrotherapy in the treatment of mental illness may be associated with an increase in neurohormone levels in the brain. The aim of the project carried on in this laboratory concerns the influence of electrostimulation on brain neurohormones; however, the present studies will be devoted only to 5-HT.

A number of investigators have reported an increase in the concentration of 5-HT in the brain following generalized convulsive electrostimulation (GES), a treatment which corresponds to electroconvulsive therapy (ECT) in clinical practice. Poloni[3,4] was one of the first to describe the effect of electrostimulation on brain 5-HT. On the basis of a biological assay procedure, in a limited study, he reported approximately a two-fold increase in brain 5-HT activity in the guinea pig following electroshock.

The most extensive study on the relationship between GES and 5-HT has been published by Garattini and associates[5-13] of the Institute of Pharmacology, University of Milan (Italy). These investigators reported a marked increase in brain 5-HT in the rat, dog, guinea pig, and rabbit 10 minutes after GES. Various analytical technics for the estimation of 5-HT concentration were employed by these workers and the magnitude of change in brain 5-HT levels that they reported depended on the assay procedure used. For example, in the rat the increase in brain 5-HT was estimated to be 2,670% by a biological assay procedure[5,6] and 66% by spectrophotofluorometric assay.[12]

In recent years Breitner[14,15] has reported the efficacy of an electric treatment, referred to as "non-convulsive diencephalic stimulation," in the treatment of mental illness. The technic involves electrostimulation in an area of the brain stem by means of an electrode inserted through the nasal cavity to a point near the body of the sphenoid bone. It has been reported to be effective in the treatment of certain psychoses, including the manic type of manic-depressives and paranoid schizophrenia, as well as neuroses characterized by anxiety and hyperexcitability.[14,15]

In view of the reports in the literature concerning the effect of GES on brain 5-HT concentration, it seemed important to investigate the possibility that localized brain stem electrostimulation (LES) might also exert a similar influence. Hence, a study was initiated to determine the effect of LES on brain 5-HT concentration in the cat and, for a basis of comparison, to determine the effect of GES on brain levels of this neurohormone in the cat and the rabbit.

Preliminary results indicated that the whole brain 5-HT concentration in the cat following GES was considerably less than that reported in the literature for other animals similarly treated. Consequently, it was desirable to determine in this laboratory the effect of GES on the brain 5-HT level in the rat, a species which has been commonly employed by other workers in similar studies,[5-9,12,13] with that of the cat. The results obtained provide the basis for this report.

Methods

Localized Brain Stem Electrostimulation (LES): The technic described by Breitner[14] for humans was modified for use in the cat. This animal was employed in the present study in preference to other animal species, because its anatomical structure facilitates placement of the nasal electrode. Cats of both sexes weighing 2 to 4 kg. were used. Each animal was anesthetized with an intravenous injection of thiopental sodium, 35 mg./kg., and a small electrode was passed through a naris, under and beyond the presphenoid to the basisphenoid at a point approximately under the sella turcica. A second electrode attached to a sponge saturated with physiological saline solution was placed on the

From the Division of Pharmacology, College of Pharmacy, The University of Arizona, Tucson.

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scalp over the parietal area. An electric current of 1 mA was delivered for 45 seconds by means of a Reiter Model RC47C electroshock apparatus in the manner described for humans.[14] Ten minutes following LES treatment, each animal was killed by an intravenous injection of air and then decapitated. The brain stem was isolated as rapidly as possible and the 5-HT concentration determined. Cats anesthetized with intravenous injections of thiopental sodium, 35 mg./kg., served as controls.

Generalized Convulsive Electrostimulation (GES): Cats, rabbits, and rats were employed in this phase of the investigation. Cats of both sexes weighing 2 to 4 kg. were used. Test animals were administered a supramaximal electroshock with 60 cycle alternating current, 150 mA for 0.4 second, through corneal electrodes by means of an electroshock apparatus similar to that described by Woodbury and Davenport.[16] Ten minutes following GES, each animal was killed by an intravenous injection of air and then decapitated. The appropriate brain tissue was removed as rapidly as possible and the 5-HT concentration in the whole brain or brain stem was determined. Untreated cats served as controls.

New Zealand white rabbits of both sexes weighing 2 to 4 kg. were used. The test animals were treated and the 5-HT concentration in the brain stem was determined in the manner described for the cat. Untreated rabbits served as controls.

Sprague-Dawley rats of both sexes weighing 150 to 200 g were administered GES as described above for the cat with the exception that the current was delivered for 0.2 second. Ten minutes following GES each rat was killed by decapitation and the whole brain of three animals pooled for each determination of 5-HT concentration. Untreated rats served as controls.

Determination of Brain 5-Hydroxytryptamine Concentration: The spectrophotofluorometric procedure reported by Bogdanski et al.[17] was used for the analysis of brain 5-HT concentration. In carrying out this procedure in this laboratory, the Amino-Bowman Spectrophotofluorometer was employed.

Results

Localized Brain Stem Electrostimulation (LES): Many of the symptoms observed in the cat during LES are similar to those observed in humans during the clinical application of this type of localized electrostimulation.[18] These symptoms include apnea, coarse tremors extending from the head to the middle portion of the body, and marked salivation and lacrimation. The apnea and tremors disappeared in the cat immediately upon cessation of LES. Localized brain stem electrostimulation was also observed to have an awakening effect on the anesthetized cat, an effect which has been observed clinically.[14,15] In addition to the above response, the cat displayed extreme miosis and, occasionally, urination and defecation. (Clinically, the patient is atropinized before electrostimulation to prevent the occurrence of the parasympathetic symptoms.[1,18]

The effect of LES on 5-HT concentration in the cat brain stem is presented in Table 1. It can be seen from this table that the concentration of 5-HT in the brain stem of LES-treated cats is essentially the same as that in the brain stem of control cats.

TABLE 1

5 - Hydroxytryptamine Concentration in Brain Tissue of the Cat 10 Minutes After Localized Brain Stem Electrostimulation (LES), 1mA for 45 Seconds.

Tissue	Treatment*	No. of Samples	Concentration of 5-HT (mcg./g. tissue ± S.E.)
Brain stem	Control	8	0.98 ± 0.035
Brain stem	LES	8	0.97 ± 0.030

*All animals anesthetized with thiopental sodium.

Generalized Convulsive Electrostimulation (GES): The results of the studies on 5-HT concentration in cat brain are presented in Table 2. A very slight increase (4%, $P>.05$) was found in the whole brain of the cat following GES, whereas a greater increase (23%, $P<.001$) was found in the brain stem.

TABLE 2

5 - Hydroxytryptamine Concentration in Brain Tissue of the Cat 10 Minutes After Generalized Convulsive Electrostimulation (GES), 150 mA for 0.4 Second.

Tissue	Treatment	No. of Samples	Concentration of 5-HT (mcg./g. tissue ± S.E.)	% Increase	P
Whole brain	Control	7	0.48 ± 0.011		
Whole brain	GES	7	0.50 ± 0.020	4%	$P>.05$
Brain stem	Control	13	0.86 ± 0.017		
Brain stem	GES	7	1.06 ± 0.041	23%	$P<.001$

The results of the studies on 5-HT concentration in rabbit brain stem are presented in Table 3. A slight increase (12%, $P>.05$) was found in the brain stem of the rabbit following GES.

The results of studies on 5-HT concentration in the whole brain of the rat are presented in Table 4. A slight increase (11%, $P<.05$) was found in the whole brain of the rat following GES.

It is of interest to note that the 5-HT concentration of the brain stem of cats anesthetized with thiopental (Table 1, Control Cats) was greater (13%, $P<.01$) than that of the brain stem of untreated cats (Table 2, Control Cats), a finding consistent with reports concerning the effect of barbiturates on other animal species.[9,10]

Discussion

This investigation was originally initiated to determine in animals the extent of alteration of 5-HT levels following electrostimulation and to compare the effects of LES and GES in this respect. In view of the observation that LES does not produce an increase in brain stem 5-HT, it is suggested that the beneficial effect of LES in the treatment of mental illness may be associated with changes in the brain other than 5-HT concentration.

In the studies involving the effect of GES on 5-HT concentration of the brain stem, it can be seen that the 5-HT concentration in the brain stem of control cats (Table 2) is very similar to that in the brain stem of control rabbits (Table 3). However, following GES, the 5-HT concentration in the brain stem of the cat was increased 23%, whereas, in the brain stem of the rabbit it was increased only 12%. This quantitative difference in response to electrostimulation may well be due to species variation, as suggested by other investigators.[6,7]

In the studies involving the effect of GES on 5-HT concentration in cat brain (Table 2), it was found that the brain stem showed a greater increase than the whole brain. The minor increase in the whole brain, as compared to that in the brain stem, is perhaps due to the relatively large mass and the relatively low 5-HT concentration of the cerebral cortex and cerebellum.

The increase in 5-HT concentration in the cat and rabbit brain following GES was considerably less than that reported for other animal species by Garattini and associates at the University of Milan.[5-13,20,21] In view of this difference, the effect of GES on the brain level of 5-HT was also determined in this laboratory for the rat, a species which has been commonly employed by these investigators in similar studies. Garattini and associates have reported that 10 minutes following GES in the rat, the 5-HT concentration in whole brain increased 66%[12] on the basis of spectrophotofluorometric assay, 121%[20] and 2,670%[5,6,20] on the basis of biological assays, and 211%[6,7,20] on the basis of spectrophotometric assay.

In this laboratory, where spectrophotofluorometric assay is employed, GES also caused an increase in whole brain 5-HT concentration in the rat. However, this increase was only in the magnitude of 11% and does not substantiate the increase of 66% based on spectrophotofluorometric assay reported by the investigators in Milan. Furthermore, their results based on biological assays have been criticized recently by Bertaccini.[22] On the basis of biological assay, Bertaccini reported that 5-HT concentration in the whole brain of the rat increased only 20-30% following GES. He emphasized that his results are at variance with those of Garattini and co-

TABLE 3

5 - Hydroxytryptamine Concentration in Brain Tissue of the Rabbit 10 Minutes After Generalized Convulsive Electrostimulation (GES), 150 mA for 0.4 Second.

Tissue	Treatment	No. of Samples	Concentration of 5-HT (mcg./g. tissue ± S.E.)	% Increase	P
Brain stem	Control	8	0.83 ± 0.039		
Brain stem	GES	8	0.93 ± 0.042	12%	P>.05

TABLE 4

5 - Hydroxytryptamine Concentration in Brain Tissue of the Rat 10 Minutes After Generalized Convulsive Electrostimulation (GES), 150 mA for 0.2 Second.

Tissue	Treatment	No. of Samples	Concentration of 5-HT (mcg./g. tissue ± S.E.)	% Increase	P
Whole brain	Control	10	0.56 ± 0.017		
Whole brain	GES	10	0.62 ± 0.016	11%	P<.05

*Each sample comprised of 3 pooled brains.

workers. In addition, Bertaccini pointed out the limitation of the spectrophotometric method for the assay of 5-HT in the brain. Udenfriend and co-workers[23] have stated that the spectrophotometric method is best suited for the assay of tissue containing relatively large amounts of 5-HT, namely, 0.04 μmole to 0.4 μmole (7-70 mcg.) of 5-HT in 500 mg. of tissue. Since the 5-HT concentration of brain tissue is considerably less than that necessary for accurate analysis by the spectrophotometric procedure, it would appear that other assay procedures are more reliable for the estimation of 5-HT in brain tissue.

The data presented herein concur, in principle, with those reported by the investigators in Milan, namely, there tends to be an increase of 5-HT in brain tissue following GES. However, the results obtained in this laboratory indicate that the degree of change in 5-HT concentration in brain tissue is considerably less than that reported by the Milan group.

Summary

Localized brain stem electrostimulation produced no change in 5-HT concentration in the brain stem of the cat. Generalized convulsive electrostimulation, however, increased the concentration of 5-HT in brain tissue of all animal species studied. These changes were in the magnitude of 4% ($P>.05$) in the whole brain and 23% ($P<.001$) in the brain stem of the cat, 12% ($P>.05$) in the brain stem of the rabbit, and 11% ($P<.50$) in the whole brain of the rat.

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A Survey of Side-effects and/or Toxicity of Newer Psychopharmacologic Agents

REUBEN M. CARES, M.D., and CHARLES BUCKMAN, M.D.*

INTRODUCTION

This study plays largely on a theme of caution, amplified and elaborated, concerning the newer drugs for mental disorders. The flood of new compounds continues unabated. There are 66 tranquilizers now on the market. The various agents are described in the literature, either by generic or brand names, or only by chemical nomenclature. This may be confusing. If there is little or no difference between two drugs in therapeutic efficiency, then their respective potential toxicity assumes importance.

It is the purpose of this paper to project the spectrum of published side-effects and/or toxicity associated with the use of the newer psychotropic agents. Our tabulation may help in the selection of a particular compound when the choice depends on toxic as well as therapeutic factors. The inventory of side-reactions may be useful not only in psychiatry but also in other specialties and in general practice.

For this survey certain limitations obtain: first, only reports with documented side-effects are considered. Secondly, older drugs that influence the central nervous system are omitted. These are the sedatives (barbiturates), stimulants (amphetamines) and other long-established drugs such as procaine, lithium salts, etc., that are now finding new psychopharmacologic applications. Thirdly, side-effects of drug combinations are not considered. We also exclude the psychotomimetics (LSD, etc.) and toxicity in experimental animals. Lastly, the range of side-effects is not intended to relate to frequency with a given compound.

The literature from 1956 to 1960 was surveyed. Neuropsychiatric and general medical journals were reviewed for the broadest possible perspective. Selection of references was based on (a) availability of English language journals, to minimize confusion with foreign equivalents for domestic generic or brand names, (b) adequacy of descriptions of adverse effects and (c) reasonably large series of cases under treatment.

CLASSIFICATION AND TERMINOLOGY

There is a plethora of synonyms applied to the newer psychopharmacologic agents. It would be unjust to compound any confusion by adding more labels. The original terms, tranquilizers and energizers, are widely understood and accepted. This is not intended to detract from other useful classifications of psychotropic drugs. Kline[28] offers a simple and detailed subdivision of the three main classes—psychoinhibitors, psychoactivators and psychotomimetics. Another grouping is that of Delay[14] who divides them into psycholeptics, psychoanaleptics and psychodysleptics. The first term includes suppressors or inhibitors; the second, the excitors; the third group comprises the psychotomimetics or hallucinogens.

For practical use we have made a table of side-effects for each of three familiar groups of drugs; namely, the phenothiazine tranquilizers, the non-phenothiazine tranquilizers and the energizers. Condensed references to the tabulated side-effects, including fatalities, are appended in the footnotes. This will facilitate the reader's inquiries on specific phases. The tables list the generic name and one example among one or more brand names. Please note that since 1956, when the A.M.A. Council on Drugs suspended this function, both the generic and the brand name are now usually coined by the producer of the drug.

Our fourth table is a compilation of all published side-effects since 1956 on a pathophysiological basis. We attempt no distinctions between side-effects and toxicity. Between the mildest transient side-effects and the toxic fatality there are too many shades of gray.

ANALYSIS OF SIDE-EFFECTS

Division 1—The Tranquilizers

(Includes antihallucinogens, ataractics, calmatives, depressants, muscle relaxants, neuroleptics, neuropharmaceuticals, neurosedatives, psychoinhibitors, psychosuppressors, psychosedatives, indeterminate psychotropic agents; omits hypnotics and sedatives.)

The synonyms listed have been applied by different authors to one or more of the same tranquilizers. One Gordian knot of semantics is Ferguson's division of tranquilizers into psychosedatives or "true tranquilizers" and neurosedatives or "mild tranquilizers."[21]

*Respectively, Director of Clinical Laboratories; Director, Kings Park State Hospital, Kings Park, New York.

TABLE 1—SELECTED REFERENCES, SIDE EFFECTS AND/OR TOXICITY OF NEWER PSYCHOPHARMACOLOGIC AGENTS

THE PHENOTHIAZINE TRANQUILIZERS

(† = number of fatalities)

	Blood			Cardiovascular				Central Nervous System				Gastrointestinal System			Skin		
Generic Name (Brand Name)	Anemia	Neutropenia &/o Agranulocytosis	Pancytopenia	Hypotension	Cerebral Anoxia	Arrythmias or Tachycardia	Other	Convulsions	Parkinsonism	Psychosis	Other	Jaundice	Hepatitis	Gastroenteritis	Dermatitis	Miscellaneous	*Comment and Special Effects*
1. Phenothiazine Group	*	*						*	*	*		*				*	Pathology of C.N.S., blood, liver[1]
		*															Lowered resistance to infections[2]
																	Review of literature[3]
2. Acepromazine (Plegicil)												*					Non-fatal jaundice[4]
3. Chlorpromazine (Thorazine)												*				*	Hemorrhages, jaundice[5]
													*				Hepatic degeneration[6]
																*	Thrombocytopenia—43 cases[7]
		*1†	*	*	*	*	*	*	*		*	*	*	*	*	*	Fever; facial edema; lactation; nasal congestion[8]
												*					Biopsy, autopsy[9]
																*1†	Hyperpyrexia, 108°[10]
																*	Galactorrhea—21 cases[11]
				*1†													7 alcoholics, severe hypotension[12]
																*1†	Uremic death, hypotensive?[13]
4. Fluphenazine (Permitil)									*								Parkinsonism[14]
		*							*	*	*					*	Akathisia, propulsion, edema[15]
5: Mepazine (Pacatal)		*														*	Diarrhea, edema, glaucoma[16]
		*1†															One death in 3[17]
																*	Menorrhagia[18]
								*			*					*	Ataxia, obstipation[19]
																*	Keratitis and conjunctivitis[20]
6. Methoxypromazine (Tentone)				*					*	*	*					*	Hypotension, rash[21]
																	Dyskinesia[22]
7. Perphenazine (Trilafon)									*		*						Toxic blindness in mental defective[23]
											*					*	Torticollis, akathisia[24]
											*						Oculogyric crisis[25]
								*									Clonic convulsions[26]
										*							Toxic psychosis[27]
																*	Menorrhagia[28]
											*						Addiction[29]
																*	Edema of tongue[30]

8. Prochlorperazine (Compazine)	*				*								*		Anemia, convulsions[31]
					*			*					*		Teratogenic effect on fetus[32]
															Oculogyric crisisfi, tonic spasms[33]
									*				*		Laryngospasm—2 cases[34]
															Catatonic states[35]
										*					Non-fatal jaundice[36]
					*			*							Opisthotonus, oculogyria[37]
9. Promazine (Sparine)	*3†		*							*					Fatty liver at autopsy[38]
				*											Arterial thromboses in 2 cases[39]
	*1†				*										Seizures in 26 cases[40]
					*			*1†							Ataxia, hypothermia; 20 yr. old[41]
10. Promethazine (Phenergan)												*			Photocontact dermatitis[42]
								*							Aphasia[43]
													*		Purpura[44]
11. Thioprozate (Dartal)												*	*		Lactation, dermatitis[45]
					*										Parkinsonism[46]
12. Thioridazine (Mellaril)													*		Amenorrhea; male impotence[47]
	*														Neutropenia[48]
					*	*	*								Akathisia[49]
													*		Transient edema, lactation[50]
13. Trifluoperazine (Stelazine)					*			*							Torticollis, dyskinesias, akathisia[51]
													*		Ptyalism—4 cases[52]
	*				*										Leukopenia, Parkinsonism[53]
14. Trifluopromazine (Vesprin)	*														Non-fatal neutropenia[54]
				*											Toxic hypertension[55]
													*		Lactation[56]
								*							Unilateral tremors—4 cases[57]
				*									*		Dysphagia, fulminating hypertension[58]
15. Trimeprazine (Veractil)					*								*		Urinary incontinence, Parkinsonism[59]

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Group A: The Phenothiazines (Table 1)

Side-effects of the first widely-used phenothiazine, chlorpromazine (Thorazine) are well known and require only brief comment. Table 1 includes 14 phenothiazine compounds in which side-reactions are described in the recent literature. The distribution of side-effects for a drug is not intended to reflect the relative frequency. Phenothiazines used for millions of patients would yield more reports than in the case of a drug tried only on hundreds, or even dozens of cases. Not too many authors itemize the percentages of side-effects, as does Weiss[51] for perphenazine (Trilafon).

Commoner phenothiazine reactions involve the blood, the central nervous system, the cardiovascular system and the endocrines. Allergic effects occur in the multiform dermatoses, transient edemas of the face or tongue and in disturbances of gastroenteric motility. One significant endocrine effect is amenorrhea, which occurred in two-fifths of Ayd's patients on large doses of chlorpromazine.[3]

The phenothiazines, as a class, cause few or no side-effects in the respiratory system, bones and joints, and urinary system. Some derivatives have been incriminated in such conditions as uremia,[36] blindness[25] and the formation of teratomas in the fetus of a pregnant patient.[40] Arterial thrombosis has been reported after regional intravenous injection.[34] These unrelated findings may be coincidental.

Excluding the widely distributed side-effects of chlorpromazine, the patterns of adverse or toxic effects differ among other phenothiazines. For example, the blood is affected more often with mepazine (Pacatal) and promazine (Sparine) than with other compounds and is not involved in five of the 14 (numbered 6, 7, 10, 11 and 15 in Table 1).

Disturbances of the central nervous system vary among four agents—fluphenazine (Permitil), methoxy-promazine (Tentone), prochlorperazine (Compazine) and trifluoperazine (Stelazine). A neuro-muscular ("neck-face") syndrome of spasm or torticollis has been seen with perphenazine (Trilafon),[45] as well as with trifluoperazine (Stelazine) and thioprozate (Dartal).[37] In one study, the neuromuscular weakness in trifluoperazine (Stelazine) therapy presumably contributed to prolapse of the uterus.[9] Tonic spasms associated with prochlorperazine (Compazine) caused dislocation of the jaws in two patients.[33]

Drowsiness or somnolence is considered either as a tolerable side-effect or simply as a pharmacologic action. This applies to a very recent phenothiazine, Buclizine[44] (not listed in Table 1). Only the occasionally used acepromazine (Plegicil) has no reported nervous toxicity.

Liver dysfunctions are rare or absent in 9 of the 14 listed phenothiazines, and are of variable severity in four, headed by chlorpromazine. The hepatitis is similar to, but milder than occurs with chlorpromazine.

Among miscellaneous side-reactions, lactation and/or swelling of the breasts has been observed in four phenothiazines—chlorpromazine (Thorazine),[11] thioprozate (Dartal),[18] thioridazine (Mellaril)[27] and trifupromazine (Vesprin).[41]

In seeking a chemical basis for side-effects, Hippius and Selbach[21] feel that it is the modification of the nucleus of the phenothiazines which accounts for side-effects, while the side-chain variations determine the therapeutic value.

A blanket verdict appears unsupported, that the range of side-effects of the several phenothiazines are identical in kind, if not degree. Further, the claim of lowered toxicity for the latest phenothiazines, is not always evident. One recent compound is R.P. 7843 (not listed in Table 1), tried in 1959 by Delay's team[15] and reported in this country in 1960 by Denber's research group.[16] The latter noted tremors, rigidity, restlessness and other phenothiazine-type of side-reactions in a good proportion of their 46 patients.

Group B: The Non-Phenothiazine Tranquilizers

In spite of different chemical composition within this group, its spectrum of adverse effects is similar in kind if not degree to that of the phenothiazines. As seen in Table 2, the non-phenothiazines likewise involve, chiefly, the nervous system, the blood, the cardiovascular system (primarily hypotension) and the skin. However, the intensity and probably the frequency are lower than in the phenothiazines.

There are nervous system effects among five of eight non-phenothiazine tranquilizers. These include convulsions, parkinsonism, ataxia, delirium and oculogyric crises.

Two are among the three diphenylmethanes and three in the miscellaneous category. With imipramine (Tofranil) therapy in 500 patients, Billig and Burris[8] found infrequent side-effects of vertigo, perspiration, eosinophilia and tinnitis. Fatal purpura has occurred with two extensively used psychopharmaceuticals—meprobamate and reserpine Rauwolfia. A low white or red blood cell count is rare among the non-phenothiazines. There is only one recent report of

fatal aplastic anemia due to meprobamate (see Table 2).

Hypotension, as the principal cardiovascular effect, is occasionally seen with meprobamate, Rauwolfia and hydroxyzine (Atarax, Vistaril). The skin is sometimes affected, with macular and other rashes described in four of eight of nonphenothiazines.

Gastroenteric disturbances occur with three compounds—two phenylmethanes and Rauwolfia, such as intestinal bleeding or stomatitis. Rauwolfia was held responsible for forming a peptic ulcer[28] or causing an existing one to bleed.[17] With reserpine, in one study of 32 patients on two or four times the recommended dose, a good minority developed fatigue, thirst and diarrhea, in one case there was an associated pulmonary edema.[29]

In the entire tranquilizer division, Groups A and B, miscellaneous signs and symptoms include pulmonary edema, chest pains and bladder incontinence.

Division 2—The Energizers

(Includes antidepressants, eudemonics, euphoriants, psychic energizers, psychoactivators, psycho-

TABLE 2—SELECTED REFERENCES, SIDE EFFECTS AND/OR TOXICITY NONPHENOTHIAZINE TRANQUILIZERS

(† = number of fatal cases)

Generic Name (Brand Name)	Central Nervous System: Blood Dyscrasias	Hypotension	Convulsions	Psychosis	Other	Gastro-intestinal	Skin	Miscellaneous	*Comments*
GROUP A: DIPHENYLMETHANES									
1. Azacyclonol (Frenquel)							*		Angioneurotic edema[1]
2. Benactyzine (Suavitil)					*				Ataxia, vertigo, dullness[2]
				*					Toxic psychosis[3]
3. Hydroxyzine (Atarax)			*1†						Convulsion, fatal coma[4]
		*							Hypotension[5]
GROUP B: MISCELLANEOUS								*	Bladder incontinence, chest pain[6]
4. Ectylurea (Nostyn)						*			Case of jaundice[7]
5. Meprobamate (Miltown)				*					Toxic delirium[8]
					*				Addiction[9]
						*			Stomatitis, proctitis[10]
							*		Morbilliform rash[11]
	*1†					*	*		600 mgm. gave fatal purpura[12]
			*						Coma with convulsions[13]
		*					*		Hypotension, rash[14]
	*1†								Aplastic anemia and purpura[15]
6. Methaminodiazepoxide (Librium)					*				Drowsiness, ataxia[16]
					*		*		Rash, dysarthria, weakness[17]
7. Rauwolfia - Reserpine (Serpasil)		*		*	*	*1†			Fatal hepatitis, parkinsonism[18]
					*				Oculogyric crisis[19]
						*			Bleeding peptic ulcer[20]
					*				Addiction[21]
	*1†								Purpura at autopsy[22]
								*	Pulmonary edema[23]
					*				Cerebral edema[24]
			*		*				Parkinsonism, convulsions[25]
8. Phenyltoloxamine (PRN)					*				Dullness, depression[26]

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analeptics, psychomotor stimulants, psychostimulants, stimulants; omits psychotomimetics or hallucinogenics.)

Eleven energizers studied are in two Classes, as entered in Table 3: I the monoamine oxidase inhibitors (MAO) and II a miscellaneous class. The MAO class, in turn, is composed of four hydrazides and two non-hydrazides. The chief hydrazide is iproniazid or Marsilid. Our survey covers the literature from 1958 to 1960.

TABLE 3—SELECTED REFERENCES, SIDE EFFECTS AND/OR TOXICITY THE ENERGIZERS

(† = number of fatal cases)

	Blood Dyscrasias		CVS	Liver		Central Nervous System					
Generic Name (Brand Name)	Anemia	Neutropenia	Hypotension	Icteric	Nonicteric	Convulsions	Psychosis	Other	Skin	Miscellaneous	*Comments*
CLASS I—Monoamine Oxidase Inhibitors			*	*				*		*	Review of side-effects[1]
			*	*				*	*	*	Review of side-effects[2]
(a) Hydrazides											
(b) Non-hydrazides											
(a) Hydrazides as a Class	*		*	*	*			*	*	*	Edema, constipation, rash, impotence, pruritis, gastritis, uremia, ataxia, twitching, dizziness[3]
1. Hydrazide Compounds								*		*	Hyperinsulism, multiple sclerosis-like picture[4]
2. Iproniazid (Marsilid)	*			*16†							Persistent treatment fatal[5]
											Hepatic injury, 34 cases[6]
										*	Pedal edema[7]
			*	*1†		*		*	*		Tremors, ataxia[8]
							*				Toxic mania[9]
3. Isocarboxazide			*								Hypotension[10]
(Marplan)			*					*		*	Metrorrhagia, epistaxis[11]
4. Phenelzine			*		*				*		Insomnia, rash[12]
(Nardil)			*								Hypotension[13]
5. Phenylisopropylhydrazine		*									Leukopenia[14]
(Catron)			*		*						Hypotension[15]
(b) Nonhydrazide Agents		*									Leukopenia[16]
6. Nialamide						*		*		*	Akathisia, chorea, diarrhea[17]
(Niamid)										*	Ptyalism[18]
7. Deanol (Deaner)							*				Toxic psychosis[19]
8. Tranylcypromine										*	Leg cramps, insomnia, nausea[20]
CLASS II—Non-Monoamine Oxidase Inhibitors			*								Myocardial infarction[21]
						*					Grand mal seizures[22]
9. Imipramine		*									Bone marrow hypoplasia[23]
(Tofranil)			*				*		*	*	Rash, tremors[24]
								*			Generalized tremors[25]
		*				*	*				Hypomania[26]
10. Methylphenidate									*		Generalized urticaria[27]
(Ritalin)										*	Hypertension[28]
11. Pipradol								*			Aggravated psychosis, insomnia[29]
(Meratran)									*	*	Nausea, rash, insomnia[30]

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1) Dis. Nerv. Syst., 21:74, 1906; 2) Bull. World Health Org., 21:397, 1959; 3) Ann. N. Y. Acad. Sci., 80: 652, 1959; 4) Ann. N. Y. Acad. Sci., 80:669, 1959; 5) J. Clin. & Exper. Psychopath., 19:178, 1960; 6) Ann. N. Y. Acad. Sci., 80:928, 1959; 7) Ann. N. Y. Acad. Sci., 80:712, 1959; 8) Am. J. Psychiat., 114:1115, 1958; 9) Am. J. Psychiat., 114:936, 1958; 10) Dis. Nerv. Syst., 21:70, 1959; 11) Am. J. Psychiat., 116:453, 1959; 12) Am. J. Psychiat., 116:746, 1960; 13) Dis. Nerv. Syst.,, 20:197, 1959; 14) Dis. Nerv. Syst., 21:67, 1960; 15) Am. J. Psychiat., 116:352, 1959; 16) Dis. Nerv. Syst., 21:67, 1960; 17) Dis. Nerv. Syst., 20:22, 1959; 18) Dis. Nerv. Syst., 20:41, 1959; 19) J.A.M.A., 172:114, 1960; 20) Am. J. Psychiat., 117:150, 1960; 21) Canad. Med. Assn. J., 82:20, 1960; 22) Am. J. Psychiat., 116:1027, 1960; 23) Am. J. Psychiat., 116:847, 1960; 24) J. Neuropsychiat., 1:77, 1959; 25) Lancet, 1(7085):1231, 1959; 26) J. Ment. Sci., 105:1123, 1959; 27) Dis. Nerv. Syst., 21:275, 1960; 28) J.A.M.A., 166:1982, 1958; 29) Zh. Nekropat. Psikiat. Moskva., 58: 600, 1958; 30) Am. J. Psychiat., 116:352, 1959.

Side-effects or toxicity are entered in Table 3.

The central nervous system is affected in eight compounds. The most serious, occasionally fatal complication, is severe liver damage with jaundice. This has been described chiefly with iproniazid (Marsilid). However, all four MAO hydrazides are associated with some degree of liver dysfunction. Convulsions occurred in four of the eleven energizers, toxic psychosis (behavioral toxicity) in three, and psychomotor and/or neuromuscular disturbances in five.

Other reported side-reactions include neutropenia or anemia with six drugs, hypotension with seven and dermatoses with six.

Apparently rare effects, among seven energizers, include diarrhea, gastritis, hyperinsulinism, metrorrhagia, ptyalism and uremia. Imipramine (Tofranil) allegedly induced myocardial infarction.[47]

The widest variety of side-effects are seen with iproniazid (Marsilid) and imipramine which are widely used. One recent nonhydrazide MAO—tranylcypromine (not in Table 3)—caused, among four patients, such effects as insomnia, drowsiness, leg cramps and constipation.[1]

COMMENT

The numerous disseminated signs and symptoms of side-reactions have been compiled in Table 4. This lists effects on the blood, cardiovascular system, central nervous system, gastrointestinal system, the skin, psychogenic and/or endocrine effects, the urinary system and an eighth unclassified column.

It is an exercise in semantics to classify, for broad acceptance, the central nervous system manifestations. These are assigned to several sub-headings—disorders of consciousness, changes in affect (or mood or behavior) and psychomotor and/or neuromuscular reactions. In our table are included Freyhan's data[22] for the phenothiazines and those of Thal[19] for the energizers, plus our own material extracted from Tables 1 to 3.

A restricted range of side-effects among 39 psychopharmacologic compounds — stressing, chiefly, the anticholinergic effects and the behavioral toxicity—has been compiled in mid-1960 by the Psychopharmacology Service Center of the National Institute of Health in Bethesda.[50] Some of these drugs we have overlooked because of inadequate documentation.

It is probable that psychogenic or psychovegetative mechanisms may produce many of the side-effects. They could well apply to manifestations in the gastrointestinal system, the skin and the endocrine glands.

Allergy plays a clear role in the skin. The mode of side-action on the cardiovascular system is unclear. Whether the hypotension and/or peripheral vascular disturbances arise (a) from direct action by the drugs[4] or (b) through psychogenic stimuli, is unsettled. It is possible that, as Assali claims for iproniazid,[2] there is venous pooling and/or lowered cardiac output from myocardial weakness.

Dosage and Toxicity

With the phenothiazines, side-effects are independent of the dose or duration of medication as shown by Cares et al.[11] and by Roizin's group.[38] Tranquilizers cause side-effects two to three times more frequently in females. In contrast, iproniazid MAO energizers show a direct quantitative relation of side-reactions to dosage.[7]

Laboratory Evidence of Toxicity

Laboratory checks will help to prevent the more serious toxic action of some tranquilizers: i.e., agranulocytosis[11,30] or iproniazid hepatitis.[7,35] Biochemical tests are of no consistent help in forecasting jaundice, except for the serum bilirubin test. Of the many liver function tests, the serum alkaline phosphatase has been studied in relation to chlorpromazine jaundice, originally by Stacey et al.[48] and more exhaustively by Cares and Newman.[10] It has been found of little value. The serum transaminase test was elevated in Scherbel's study of 10 patients on MAO drugs.[42]

There is a difference in the pathology of liver damage caused by tranquilizers or by iproniazid (Marsilid) energizers. With the former, the jaundice is due to intralobular biliary stasis, while iproniazides cause liver cell damage or necrosis as in acute yellow atrophy.

Also, the purpura of meprobamate is independent of blood platelets[12] as it is in chlorpromazine.[13,32] However, Shawver and Tarnowski[46] found low platelet counts with chlorpromazine in 15% of 245 patients. The purpura of the reserpine-Rauwolfia derivatives is usually thrombocytopenic.[43]

The allergic reactions are not usually supported by eosinophilia although Kuhn[31] reports mild eosinophilia in two-thirds of 500 cases given imipramine (Tofranil).

A comprehensive study of the pathologic tissue changes with the phenothiazine tranquilizers by Roizin et al.,[38] indicate these to be sporadic or inconstant, except for the bone marrow and liver. Brain findings are nonspecific, inconstant and mild. Pathologic material on 13 fatalities asso-

ciated with psychotropic drugs was recently collected by Roizin and six other pathologists[39] from over 45,000 patients treated in 26 mental hospitals in New York State. They observed four main groups of toxopathologic findings—blood dyscrasias, toxic hepatitis, nonicteric hepatitis and nonspecific neuropathology.

Electroencephalographic changes occur but are

TABLE 4—PATHOPHYSIOLOGICAL MECHANISMS IN PUBLISHED SIDE EFFECTS AND/OR TOXICITY OF NEWER PSYCHOPHARMACOLOGIC AGENTS

1. BLOOD

A. ERYTHROPOIETIC DISORDERS
- Anemia
- Aplastic anemia

B. LEUKOPENIC DISORDERS
- Agranulocytosis
- Leukopenia (neutrophenia)

C. HEMORRHAGIC DIATHESIS
- Bleeding of nose, gums, conjunctive, gastro-enteric system, lungs, skin.

2. CARDIOVASCULAR SYSTEM

A. DISTURBED CARDIAC OUTPUT
- Asphyxia
- Cardiac failure (dyspnea)
- Edema (facial, pedal)
- Hepatomegaly (passive congestion)
- Hypertension
- Hypotension
- Pulmonary edema

B. DISTURBED VASCULAR FUNCTION
- Coronary occlusion (myoinfarction)
- Epistaxis
- Thrombosis (arterial, venous)

C. DISTURBED CARDIAC RHYTHM
- Arrythmia
- Bradycardia
- Tachycardia

3. CENTRAL NERVOUS SYSTEM

A. DISORDERS OF CONSCIOUSNESS
- Confusion
- Coma
- Drowsiness
- Insomnia
- Syncope (cerebral anoxia, neurocirculatory collapse)

B. AFFECTIVE CHANGES AND/OR MOOD
- Agitation (excitement, irritability)
- Anhedonia
- Anxiety
- Depression (dullness, hypomania)
- Euphoria
- Lethargy
- Mania
- Psychosis (drug induced)
- Retardation (withdrawal)

C. PSYCHOMOTOR AND/OR NEUROMUSCULAR REACTIONS
- *Akathisia
- Akinesia
- Ataxia
- Convulsions
- Catatonic state of rigidity
- Choreiform movements
- **Decerebrate movements
- Dyskinesia
- Hyperreflexia
- **Ocular palsy (oculogyria, diplopia)
- *Propulsion
- *Torticollis
- Restlessness (turbulence)
- *Tremor (local or diffuse)
- Trismus
- Twitching

D. UNCLASSIFIED
- Amblyopia
- Aphasia
- Cerebral edema
- Drug addiction
- Drug tolerance
- Equilibrium disturbance
- Glaucoma
- **Hyperthermia
- **Hypothermia
- Kerato-conjunctivitis
- Neuralgia
- **Opisthotonus

4. GASTROINTESTINAL SYSTEM

A. CHANGES IN PERISTALSIS
- Constipation
- Dysphagia
- Diarrhea (hyperperistalsis)
- Epigastric distress (gastralgia, pyrosis)
- Nausea
- Vomiting

B. SECRETORY CHANGES
- Dry mouth
- Peptic ulcer (bleeding)
- Ptyalism (sialorrhea, drooling)

C. PARENCHYMAL DAMAGE
- Hepatitis (icteric, non-icteric)
- Hepatic necrosis

D. INFLAMMATIONS
- Gastroenteritis
- Gastritis
- Proctitis

E. UNCLASSIFIED
- Anorexia
- Abdominal rigidity

5. SKIN

A. NEUROGENIC
- Hyperaesthesia
- Paraesthesia
- Pruritus
- Sweating

B. ALLERGIC
- Dermatitis
- Urticaria
- Photosensitivity

C. UNCLASSIFIED
- Trophic ulcers

6. PSYCHOGENIC AND/OR ENDOCRINE

A. GENERAL
- Diabetes mellitus (aggravation)
- Hypereroticism
- Hyperinsulinism
- Hypoadrenalism (fatigue)
- Impotence
- Polyuria
- Weight gain

B. FEMALE DISORDERS
- Amenorrhea
- Lactation (swollen breasts)
- Menorrhagia
- Metrorrhagia

7. URINARY SYSTEM
- Delayed micturition (retention)
- Incontinence (or dribbling)
- Nephrosis
- Uremia

8. MISCELLANEOUS
- Arthralgia
- Edema of tongue
- Fatigue
- Myositis
- Nasal stuffiness (allergic?)
- Potentiation of other drugs
- Susceptibility to infection
- Teratogenic effect on fetus
- Weakness

* Parkinsonism, extrapyramidal and central ganglionic effects.
** Midbrain effect?

not specific for the phenothiazines.[6] Chlorpromazine induced deviations in the EEG in patients with a convulsive tendency.[5] Among the energizers, uncharacteristic changes in the EEG have been reported only for the principal hydrazides (Marsilid, etc.).[23]

Counteraction of Side-Effects

A number of antidotes are available where continued medication is desirable. There has been success in combating the dry mouth and hypotension of promazine (Sparine)[46] or the side-effects of the phenothiazine group,[28] or those of reserpine.[20] The adverse effects of the energizers may be also offset.[21] Kline's recommendations include reduction or stoppage of dose and substituting related compounds free of the particular side-effects encountered. One can afford symptomatic relief by a pharmacologic antagonist, ACTH (or for use with tranquilizers), glutethimide (Doriden). For office patients especially, who drive while under the influence of a tranquilizer (or energizer), traffic hazards can become a serious problem.[19]

SUMMARY AND CONCLUSIONS

1. The variety of side-effects may have no relation to the therapeutic efficiency of a particular psychopharmacologic compound. The range of these side-reactions does not necessarily reflect the frequency of complications.

2. Side-effects and/or toxicity of the newer psychotropic agents are divided into three groups, as based on three comprehensive tables:

(a) The phenothiazine tranquilizers cause side-effects commonly involving the central nervous system, the blood (neutropenia), cardiovascular system (hypotension), the gastrointestinal system (hepatitis), skin, and to some degree, the endocrines (menstrual disturbances).

The several compounds in this chemically-related group differ somewhat in intensity and distribution of their several side-effects. These may occur as single or multiple effects in varying patterns of signs and symptoms.

(b) The non-phenothiazine tranquilizers show a spectrum of adverse effects which is similar in variety and localization to that of the phenothiazines. The intensity of these effects is less pronounced; also, the frequency is probably lower for most of the widely used agents in this group.

(c) The energizers, particularly the iproniazid derivatives, have as chief side-effects, hepatic damage which is, occasionally, severe or fatal, plus milder effects on the central nervous system. Rarer instances of side-reactions elsewhere are similar in distribution to the tranquilizers.

3. The tabulated range of the unwanted effects and/or toxicity may help to determine whether signs and symptoms that appear during therapy are due to the drug or to simple coincidence.

4. The nature of the various side-effects and their tolerance are factors governing the choice of drugs. A second choice may be indicated when therapeutic efficiency is approximately equal.

5. It would appear that the side-effects and toxicity of these newer drugs for mental disorders are no greater in frequency or severity than for many other classes of pharmaceuticals, both in psychiatric and non-psychiatric diseases. Toxic neutropenia and hepatitis occur with many therapeutic agents used in general medicine.

6. Prevention or reduction of side-effects or toxicity is aided: (a) by judicious screening of available tranquilizers or energizers; (b) often by pharmacologic antagonists or other antidotes; (c) by laboratory checks. With tranquilizers, the side-effects are usually not related to dosage or duration; with energizers there is some correlation of dosage to the incidence of side-reactions.

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The Antidepressant Qualities of Elavil

EDWIN DUNLOP, M.D.*

The zenith of introduction of antidepressant agents was reached in 1959 when at least five antidepressant agents were made available for the treatment of depressions. Listed alphabetically, but not necessarily in order of appearance, they were:

Catron, Nardil, Niamid, Marplan, Tofranil.

It was at this time that a substance MK-230 was offered to me reputed to have antidepressant and also some tranquilizing properties. My earliest experience with it proved disappointing because I was looking for an improvement on the five excellent antidepressants already available, and in comparison with these drugs, there did not seem to be a promptly produced and consistently maintained antidepressant effect. An objectionable feature was the complaint of drowsiness and my interest was not too enthusiastic. However, as is well established by now, many of the monoamine oxidase inhibitors of the irreversible hydrazine group gave rise to side effects mostly manifest by hypotension, and in a few cases produced a hypomanic state, which was easily controlled by reduction of dosage and by combining a phenothiazine compound in the treatment program.

The complaint of hypotension always seems more marked in the elderly patients, and these also did not show exactly the same type of acute depressive picture that one is apt to meet in middle aged melancholia. It is now common knowledge, and no doubt common practice, that the monoamine oxidase inhibitors have an antidepressant effect in the great majority of properly selected cases—as does electrotherapy. However, there are many depressive syndromes which do not recover with electroshock therapy and occasionally patients are made worse by this therapy.

From the very beginning many people considered the antidepressant drugs equal in value to electroshock as a reliable and rapid method for treatment of most endogenous depressions. Others were not so optimistic. At this time a proper perspective has now been obtained. In my opinion, the antidepressant agents offer a wider range of usefulness than does electroshock, but, as we know we often failed to establish recovery where we felt we had expected good results.

*Director of Research, Fuller Memorial Sanitarium, South Attleboro, Mass.

The antidepressant agents are an added agent in the treatment of depressions including many of the atypical depressions which do not respond or have responded unsatisfactorily to electroshock. Patients who do not improve with electroshock have atypical depressions that do not have the markings of the endogenous type such as early wakening, diurnal variation of mood, stable personalities, psychomotor retardation, self reproach and intense feelings of guilt. Their depression seems secondary to other neurotic or pseudoneurotic complaints and tendencies. As a rule their life history does show a tendency to a course that we might call psychosomatic distress; frequently they have had previous admissions to hospitals for vague and undefined complaints. They never seem to get completely over whatever ailment was plaguing them and yet go through life with reasonable success. When their depression fully ripens, they are not plunged into the abysmal depths of despair, morbid thinking or utter futility of the melancholic. Clinically, therefore, their behavior does not show the sharp distinction which is so characteristic of the endogenous depression.

With advancing knowledge and information in general practice and other divisions of medicine, and even in the general population and other specialties there is earlier referral of psychiatric problems. This may be the reason why we are not seeing the acute depressions that we formerly found. When cases are referred they are only moderately depressed and respond more readily to less drastic therapy. Ultimately it can be expected that there will be greater use of these antidepressant agents, in correctly diagnosed cases by general practitioners and internists. Psychiatrists can no more expect to monopolize antidepressant therapy, in chemotherapy or electrotherapy, than the cardiologist in the use of electrocardiogram and anticoagulant agents. As more data are accumulated, we can all learn where our errors in the use of chemotherapy were most frequently made and to avoid these mistakes.

Many depressions in the so-called geriatric population have been presumed to relate to associated cerebral vascular disease. Very often there is moderate hypertension, symptoms of anxiety associated with depression, insomnia, lightheadedness, dizziness, palpitation, difficulty in con-

centration, fear and foreboding about the future, with a tendency to regard all these symptoms as the beginning of the end. Many of these complaints are relieved with careful handling of the patient along with general terms of reassurance and modified any existing hypertension with available therapies. Often redirection of the patient's interest into a worthwhile and productive life dispells the notion that the patient is doomed to remain in his present state.

In contrast to this where arteriosclerotic disease exists (evidenced in the retina, etc.) the depressive syndrome is more dramatic, often accompanied by paranoid ideas, tense feelings of guilt and sinful behavior, rumination over misdeeds of the past (usually exaggerated and sometimes imaginary) with preoccupation with every ache and pain to which the patient is subject at that age. In most of these cases as a contrast to the first group, there is evidence of intellectual impairment, lack of concentration, and a poor memory for recent events, associated with ideas of hopelessness.

In comparing Elavil with other antidepressant agents, it is quickly apparent that it has a close identification with Tofranil. The exact mode of action of Elavil is not yet known and we might say the same of Tofranil, but it is probably a weak monoamine oxidase inhibitor. Elavil has a structure closely resembling imipramine (Tofranil). A comparison of molecular composition shows marked similarities in the three-dimensional geometry of these molecules with regard to the angles between the components of the ring systems and the relationship of the side chains to the seven-membered rings.

There seems to be less side effects with Elavil than with Tofranil and there was not a preponderance of complaint of sweating. With Elavil there is a little more tendency to drowsiness than with Tofranil. Most patients on Tofranil would complain of drowsiness, but with Elavil two tablets, t.i.d. (a total of 150 mg. daily), drowsiness was so severe as to require the patient to lie down and very often sleep during the day. However, patients usually adjust to this, especially the hospitalized group, and with persistence, doses of 150 mg. daily, within four or five days, are well tolerated.

I believe that patients on Tofranil on the recommended dosage of 25 mg. q.i.d. show a more rapid improvement than with Elavil in the same dosage. Elavil satisfactorily controls the anxiety, tension and psychosomatic distress so commonly accompanying a depression in the middle age and geriatric group. Because of the lag period associated with all the current antidepressant agents, few show any degree of improvement within the first five to seven days, with perhaps the exception of those on alpha-ethyltryptamine (Monase). I first prescribe a rapid acting analeptic such as Ritalin, Ambar, Dexamyl or Methedrine as indicated, even where there might be some evidence of hypertension, with a systolic pressure in excess of 180. I believe that the beneficial alterations of mood outweigh any disadvantage that these stimulants may potentially have to elevate the systolic pressure. With this combination, the patient immediately feels some improvement. I have long advocated that no matter how good the antidepressant chosen may be, one cannot expect patient endurance and patience to hang on for the seven to ten days or longer without some improvement in mood. Where we have relatively simple, innocuous and reliable agents such as the analeptics mentioned which shorten the recovery period and bridge over a dangerous gap we should put them to use.

I have been interested in Elavil particularly because of its availability in parenteral form. I have used the intravenous method of administration a great deal since this was reported by Henry V. Agin. In many patients showing mixed pictures of anxiety and depression, 20 to 30 mg. of Elavil given intravenously produced a calming effect comparable to that produced by amobarbital. The effect is sustained for 36 to 48 hours and no euphorizing or hypomanic activity has followed. Systolic blood pressure changes have not varied more than 20 mm. and in no case has hypotension been a problem.

I have treated many elderly people by intramuscular or intravenous administration of Elavil to reverse the course of their depression rapidly. In some cases the result has been dramatic, not equaled by electroshock or monoamine oxidase inhibitors administered for six weeks.

Summary

Elavil seems to act as a broad spectrum antidepressant. It does not have the specific incisive qualities of some antidepressant agents, but I do believe for what it is lacking in rapidity and perhaps selectivity of action, it gains in producing only minor side reactions. To date no liver damage, severe hypotension, peripheral neuritis, gross weight gain or edema has occurred. Such side effects are often seen in patients making excellent clinical recovery on iproniazid.

Conclusions

In a study of 62 patients presenting cardinal symptoms of depression, 50 were atypical depressions which were not expected to respond, or did not respond satisfactorily, to ECT. These patients showed gratifying results when treated with Elavil. Following recovery, maintenance therapy was continued a minimum of five months and for 12 months in some cases. Side effects were minimal compared with the effectiveness of the drug.

Elavil was combined with electroshock in 12 patients without complications. There was no potentiation of sedative medication required to control insomnia. Clinical recovery was accompanied without over-stimulation, hypomania, or excitability. Elavil has proved to be a specific form of therapy for the treatment of atypical or secondary depressions, and can be administered intramuscularly or intravenously to hasten the patient's recovery. It has maximal efficacy in those cases presenting a marked anxiety level associated with depression.

Case 4601—M.I.H.: This 43-year-old man had attempted suicide by firing a .22 calibre revolver through the roof of his mouth. The slugs had not entered the brain but lodged in the bone structure of the base of the skull. He admits having been depressed for six months following surgery for a renal calculus which rendered him impotent. He admitted hearing voices for the last three months. He had been unable to work and spent most of his time in the seclusion of his home, doing odd jobs in the cellar. He had given up all social activity.

He was given amitriptyline (Elavil) 25 mg. 1 q.i.d. and a mild sedative. By the end of the first week, he communicated much more freely, expressed the desire that he wished he had sought help early, admits that his mind is full of bad thoughts, and that he wants to do something about them. The patient continued to improve quite rapidly and was discharged on the fifteenth hospital day. There has been follow-up on an outpatient basis. He remained on 75 mg. of amitriptyline for six weeks, then reduced to 50 mg. daily which he is currently taking.

The patient has returned to his former employment, has done very well, and there appears to be no evidence that his depression has returned.

Case 4196—M.B.S.: This 70-year-old woman was in the third recurrence of a psychoneurotic or secondary depression. In 1957, she had been given electroshock therapy, and following seventeen treatments at the State Hospital, had made some improvement. A year later she was readmitted to the Fuller Memorial Sanitarium, again very depressed.

At this time, she was put on a powerful monoamine oxidase inhibitor and made sufficient improvement to be discharged but she was not well. She was continued on the monoamine oxidase inhibitor for four or five months with gradual reduction in dosage. She expressed the opinion that the medication had materially improved her arthritic condition but her depression persisted.

In June 1960 she returned again depressed. She was given intravenous amitriptyline (Elavil) 30 mg. daily i.v. and 25 mg. q.i.d. p.o. By the end of the first week she was considerably improved and felt less depressed. She no longer spoke of the multiple psychosomatic complaints, cancerophobia, and was no longer preoccupied with "a mental breakdown." Intravenous medication was discontinued after one week, and she was continued on oral medication for another two weeks. At this time, the patient was discharged. She has been maintained on 50 mg. daily and reports that she has been better following this treatment, than on 17 EST's two years ago and the one year on the monoamine oxidase inhibitor. Elavil apparently accelerated her recovery, and the combined intravenous and oral usage of the medication was of definite value in the treatment of this patient.

Case 4598—I.T.M.: This patient had been hospitalized at a state hospital for a depression three years before and responded to EST. therapy. Her depression recurred, and she was admitted as a private patient to Fuller Memorial Sanitarium. She presented a picture of complete dejection, apathy, and depression. She could not speak above a whisper. There was marked psychomotor retardation. She had not been eating or sleeping well, had lost interest in everything, and expressed the idea that she didn't wish to live.

An A.N.S.R. was done on this patient, and it showed a characteristic high rise of adrenalin response. No response whatsoever to mecholyl. I did not believe that she would respond to EST. The patient was given amitriptyline 25 mg. p.o. q.i.d. After a week, she still seemed depressed, and EST was given despite the negative findings of the A.N.S.R., although clinically she was markedly depressed.

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Organic Therapy in Pediatric Psychiatry

LAURETTA BENDER, M.D.* and GLORIA FARETRA, M.D.**

Since March 1956 children from the ages of 4 to 15, both male and female, have been treated in the Children's Unit of Creedmoor State Hospital. About 80 to 90 per cent of them have received medication or some other form of physiological therapy during the course of their hospitalization. In addition many continue to receive medication in the after-care program.

Our primary consideration in selecting treatment methods for children is use of a rapid intensive adequate program. The developing child is constantly learning and confronting new experiences which are unique to childhood. If, for some reason, he cannot benefit from the experiences of these years they are in a sense lost to him. A child who is prevented from developing normally due to organic or psychological problems is further delayed in his maturation because he is unable to profit adequately from his environment. Physiological therapies are among the best methods of obtaining this goal. They are generally effective quickly; they stimulate the child's own potentials and allow him to benefit from socializing, schooling and other childhood events.[1]

The tranquilizing drugs are only a small part of the picture. In general we do not want to "tranquilize" the children or merely to eliminate one or two difficult symptoms, such as aggression or hyperactivity. We want to help the child develop, to organize and pattern his behavior, to reduce learning difficulties (e.g. by helping to increase his concentration span), to improve interpersonal relationships. Often we want to stimulate the child, even to make him more aggressive, though this may at times distress ward personnel or others in charge of the child's care.

Our choice of drug is based on the child's need and on which medication, in our experience, seems best to treat those needs. We vary dosages or add other medications, depending on the child's response. It is important to try these methods before deciding to change medication, since the drug may produce a delayed response, or may even temporarily show adverse effects. We have noted that children under 12 can be given relatively high dosage, even equal to adult dosage. As the child progresses into adolescence, dosage and reactions to the medication become similar to that of adults.

When medication is started on a child the same difficulties occur which are often reported in therapy of adults. For the first few days there are complaints that the child is "too sleepy" or "too active," that the drug is ineffective, etc. There is also a tendency to blame every change in behavior on the drug whether good or bad. We have noted one reaction which occurs especially with phenothiazine, occasionally with reserpine. For the first week or two the patient seems more disturbed. He appears more anxious, more active, begins to talk about his symptoms more freely and in general gives the impression that he is experiencing more difficulties, e.g. there are children who may have been hallucinating prior to therapy but talk much more freely about the hallucinations when first started on the medication. This reaction usually subsides and the patient begins to respond with a decrease in his symptoms.

We have noted no serious or irreversible side effects from any drug. There has been no incidence of jaundice and no blood dyscrasias. Occasionally a child becomes excessively drowsy during the first few days. There have been a few mild allergic reactions. Phenothiazines occasionally produce mild muscular spasms and tremors which are readily controlled by stopping or decreasing the medication, or by giving anti-Parkinson drugs. We do not give barbiturates to the children since we have noted that they increase rather than decrease the child's activity and anxiety and produce other unfavorable symptoms. At times we have found that taking the child off medication after a long period of receiving drugs has been especially beneficial and may in itself result in relief of symptoms.

A summary of the drugs we have used most commonly, with indications and dosage, follows:

PHENOTHIAZINES: Best in schizophrenic patients who are disorganized, anxious, showing neurotic symptoms, especially hallucinations and introjected bodies, poor reality contact.

Effective in catatonic or "typical" adolescent schizophrenics.

Good in aggressive children, especially when combined with reserpine. Organic children occasionally show lowered convulsive threshold. Not so effective in organics.

*Director of Psychiatric Research, Children's Unit, Creedmoor State Hospital, Clinical Professor of Psychiatry, Columbia University, New York.

**Associate Research Scientist, Child Psychiatry, Creedmoor State Hospital.

Thorazine: Usual doses, 100 mg. to 1000 mg. a day.

Compazine: 20 to 80 mg. a day.

Stelazine: 2 to 8 mg. a day. More stimulating. Seems promising for autistic children. More side effects.

Sparine: 100 to 1000 mg. a day. Better for control of motor symptoms.

Benadryl: 40 to 400 mg. a day in a disorganized, younger child, including organic children.

RESERPINE: .4 mg. to 8 mg. a day (higher doses in severely disturbed children). Among the best drugs for autistic children. Often combined with one of the Phenothiazines. Very good in disturbed, disorganized, "psychotic" children. Helpful in organic children.

MEPROBAMATE: 1600 to 4800 mg. a day. Disorganized, anxious, hyperactive children, especially the organic, with or without anti-convulsants.

PROZINE: (Equanil plus Sparine)—4 to 8 capsules a day. Excellent in controlling behavioral symptoms, especially the organic children.

BENZEDRINE: Up to 20 mg. a day. Hyperactive, organic younger children. Learning disabilities. Sexual problems and preoccupations.

ENERGIZERS: (Niamid, Nardil, Tofranil, etc.)—Seem promising in withdrawn, depressed adolescents, and autistic children. Tofranil especially seems to be promising in autistic children; they are more alert, make attempts to speak, begin to relate.

LIBRIUM: 20 to 80 mg. a day. Similar in indications to meprobamate. Not more effective.

DEANER: There are many reports that it stimulates learning and controls behavior, but we have found it relatively ineffective.

ANTI-CONVULSANTS: Dilantin, Tridione, Mebaral, Mysoline, etc.—often combined with meprobamate, sometimes with reserpine, Prozine, benzedrine. Used in organic behavior disorders or children with positive EEG's, even without convulsions.

Electroshock therapy in certain cases still seems to be the most effective and most rapid treatment.[2] There are three main indications for considering electric shock as the treatment method, though other children who do not fit into these groups also may benefit from shock treatment. (1) Autistic children preferably under the age of six. (2) Children ages 7 to 10 with a pseudo-neurotic picture, severe anxiety and disorganization. (3) Adolescents with an acute episode of schizophrenia, especially the catatonic type, or those who are seriously disturbed, anxious and agitated, out of contact, or hallucinating.

Our results in these cases have generally been good, with rapid remissions and over-all improvement. Even the most regressed and disturbed children at least show better patterns of behavior, eating, relating, etc. As with drug therapy, children who are in the process of receiving shock treatments often seem worse before they are better. An important effect with this therapy is stimulating maturation in autistic and other young schizophrenic children. Therefore results may not be noted for several months to a year. Follow up studies have shown no detrimental effects on psychometrics, EEG, neurological tests, etc.[3,4]

Sub-coma insulin is being given to a group of children on the Children's Unit. It is apparently helpful in some cases but our experiences with this therapy are too new for thorough evaluation. The effect of alternating pressure chambers is also being studied.

Although we are convinced of the value of physiological therapy in child psychiatry, we do not feel that it is sufficient in itself. The children in our unit must have a structured program with organized activities, school, occupational and recreational therapy, and general medical care. Group and individual therapy are important in some cases. Close contact with the family and community, especially by weekend and school vacation visits, are strongly encouraged. Release from the hospital occurs as early as possible, with after-care and often continuation of medication an essential part of the total treatment program for our children.[5]

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Use of Glucagon in Insulin Coma Therapy

H. Peter Laqueur, M.D.,* and Harry A. La Burt, M.D.**

The use of Glucagon in insulin coma therapy and a short review of the other modifications of insulin coma therapy which have been developed in the insulin unit at Creedmoor State Hospital over the past ten years will be discussed. The method has been simplified to a degree that now 50 patients may be treated safely by the same crew which formerly would take care of between 17 and 30 patients. An increase of case load to 60 or even 75 patients with the addition of only one or two attendants or nurses is possible.

In more than 500 patients treated with insulin coma therapy in the last ten years not a single fatality nor a prolonged coma has occurred although patients are induced to deep third stage (early red stage in our own terminology) coma. Only two or three times has there been delayed awakening, the longest delay having been 3½ hours.

This formerly complex treatment which was not without danger and risk can now be carried out as safely as ECT or treatment with tranquilizing drugs in high dosages.

Our results with the new simplified method are good and we do not hesitate to recommend the use of insulin coma therapy to the families of schizophrenic or involutional paranoid patients who formerly might have considered insulin coma therapy only after all other possibilities of extramural treatment had been exhausted.

The main modifications of technique are:

1. A multiple dose insulin technique with diet control and with the newest addition of D.B.I. sensitization of patients to lower their insulin requirements.
2. Termination of coma by intramuscular injection of Glucagon or of a combination of adrenalin and thiamine.

The multiple dose insulin technique combined with a strict control of the diet was reported for the first time at the A.P.A. Meeting in Philadelphia in April 1959. The objective is to obtain yellow stage coma (involving symptoms pertaining to pons and cerebellum) with a minimum dose of insulin, thereby reducing the incidence of secondary hypoglycemic reactions in the afternoon to about one tenth of what it usually is with the classical massive single-dose method. Consequently the patients are lucid on treatment afternoons and more receptive to psychotherapeutic work than the usual insulin patient. This made it possible to organize the insulin ward as a "therapeutic community" including such features as patient government, patient-family meetings and intensive group therapy, thus contributing to the patients' psychological and social rehabilitation.

Multiple insulin injections are given at 7:00, 7:15 and 7:30 a.m. and coma is achieved 10:30 and 11:30 a.m. Most comas are yellow stage of at least one hour's duration. Patients are permitted no more than beginning red stage levels (medulla oblongata) for a few minutes before termination of the coma is begun.

In former years the dosage level was about 60 to 80 U. total. Today it lies a little higher, at 100 U. The reason is simply that in former years termination of coma by i.v. injection of glucose awakened the patients in a few minutes, while now terminations are almost exclusively by i.m. injections requiring from 20 to 30 minutes.

Since time is limited because of personnel problems and shortening the duration of coma is not desired, the 30 minutes needed for the i.m. termination is compensated for by shortening the time between the insulin injection and the onset of coma. The only way to do this is by slightly increasing dosage levels. There seems to be a direct relation between the length of time interval from injection to onset of coma on one hand and the dosage on the other. The shorter this time interval, the higher the dose of insulin must be to achieve the desired depth of coma.

Other modifications of insulin coma therapy are under study. Some of these were reported at the meeting of the American Society of Medical Psychiatry in May 1960.

One of the most promising studies is the use of semi-lente insulin to induce deep hypoglycemic coma. With an injection of this slowly absorbed insulin at 4:00 a.m., patients go into coma between 8:00 and 10:00 a.m. and one can lower the dose 20% from the normal level of the multiple dose technique.

Semi-lente insulin technique may very well be that of the future because it permits patients to have all the advantages of night- and early morning treatment and keep practically all day available for psychotherapeutic work. However,

*Supervising Psychiatrist in charge of Insulin Research and Teaching Unit.
**Director Creedmoor State Hospital, Queens Village, New York.

it requires at least one well-trained nurse on the night staff.

The main topic of this presentation concerns termination of insulin coma by intramuscular injection. Glucagon is used for this purpose as well as a technique by i.m. injection of a combination of adrenalin and thiamine. The adrenalin-thiamine technique was developed in an attempt to find a substitute for Glucagon should the latter not be readily available.

While evolving the multiple dose technique, it was noted that an injection of ⅛ to ¼ mg. of adrenalin lightens a red stage coma (medulla) to a yellow stage (pons and cerebellum). In experiments with Glucagon, it was found that 100 mg. thiamine i.m. given additionally, speeds and enhances the awakening effect of Glucagon. With these two observations in mind, termination of coma at first with adrenalin alone was attempted. Only in 50% of comas was it successful and then with difficulty although doses up to 1 mg. i.m. were used. Different compositions of adrenalin and thiamine were used. Thiamine alone has no effect on hypoglycemic coma. The combination of adrenalin and thiamine is effective most probably because the acid co-enzyme thiamine prolongs the life of adrenalin in the tissues while adrenalin without addition of thiamine is rapidly destroyed by deamination.

Double-blind studies with Glucagon as well as with adrenalin-thiamine combinations were carried out in order to determine the lowest effective dosage levels in both techniques.

TABLE I

Glucagon

(Intramuscular Technique)

Total comas treated with Glucagon: 1894

Success with Glucagon: 1623—85.7%

Cases where second dose was necessary: 106—5.6%

No. Cases	Dosage mg.	% Successful
227	1/8	67.4
239	1/4	88.3
626	1/3	89.8
662	1/2	83.8
37	3/4	97.3
73	1	94.5
30	2	90.0

Our findings indicate that the optimal dose of Glucagon is 1/3 mg. and if within 20 minutes the patient is not awake, a second injection of 1/3 mg. of Glucagon is given i.m. The use of more than 2/3 mg. is unnecessary because if two successive injections of 1/3 mg. Glucagon each are not effective, additional administration of this substance will have no more effect and termination by i.v. glucose is therefore indicated.

This is a report on the termination of 626 comas with 1/3 mg. Glucagon in which awakening occurred in approximately 89.8% with only infrequent need of a second injection. In a special double-blind study 50% of the patients responded with no more than 1/8 mg. of Glucagon. This indicates that if necessary 40 to 80 comas could be terminated with a single vial of 10 mg. Glucagon.

Studies with adrenalin-thiamine have shown that optimal results are being achieved with a combination of 2/3 mg. adrenalin and 33 mg. thiamine in one injection. Also with this technique rather infrequently a second injection of the same dose is necessary. We can terminate approximately 80.5% of comas with this method.

TABLE II

Adrenalin and Thiamine

(Intramuscular Technique)

Period: 12/30/59—10/10/60

	Success with 1 injection	Success after 2 injections	Failures	Total
½ mg. Adrenalin 50 mg. Thiamine				
12/30/59—2/25/60	170	18	40	228
2/3 mg. Adrenalin 33 mg. Thiamine				
2/15—4/15/60	426	94	94	614
4/18—6/ 6/60	444	66	122	632
6/ 7—7/29/60	301	101	160	562
9/15–10/10/60	286	57	60	403
TOTAL:	1627	336	476	2439
Total Percentage	66.7%	13.8%	19.5%	100%

The failure of patients to respond to Glucagon and to the adrenalin-thiamine combination is more a matter of individual patterns than of dosage. It seems that a relatively small percentage of patients (10-15% apprx.) can be aroused from deep coma by no other known method than the introduction of glucose either i.v. or by gavage.

Although Glucagon frees glucose from the liver while the adrenalin-thiamine combination frees glucose from the liver and the muscles, the effects of both substances are clinically very much alike. In double-blind studies neither doctors nor nurses were able to discern which patients had had Glucagon and which adrenalin-thiamine.

The termination of insulin coma by i.m. injection is safer because the risks inherent in i.v.

injection of glucose or gavage are avoided. A new factor for psychiatric investigation of patients is also available. During the 20 to 40 minutes awakening period after i.m. termination —as contrasted to the 1 to 3 minutes awakening after i.v. injection of glucose—the patient passes through a stage of semi-consciousness which has been profitably used to explore preconscious and sub-conscious processes that the patient blocks out when fully conscious. Insufficient personnel are available to obtain the maximum value of this uncensored information offered by the patient during these awakening interviews, but that obtained helps significantly in directing individual- and group-therapeutic efforts.

A word of caution must be added. If these techniques are to be effective, it is absolutely necessary that nurses and attendants work actively with the patient as soon as they see the first signs of arousal from deep coma after the i.m. injection of either Glucagon or adrenalin-thiamine. If the high point on the blood sugar curve following the injection is missed (it is usually reached after 10 to 15 minutes), the patient tends to slip back into deep coma and then requires a second injection. However, not even a second injection will awaken him without the active help of attendants and nurses.

On the other hand, if after the first signs of arousal, the patient is actively stimulated to drink a cup of molasses, even though he may not yet be fully conscious, his awakening will then progress further to the point where he can get up and have breakfast. It really depends on the dedication and activity of nurses, attendants and student nurses whether intramuscular termination techniques are effective. With an interested and willing crew these techniques have succeeded over a period of 15 months in many thousands of comas.

The nurses and attendants also stimulate the patient to make an active effort himself to waken. This is in contrast to the awakening "with a bang" by i.v. injection of glucose and it is our impression that this active effort on the part of the patient contributes psychologically to the value of treatment. Similar observations were already made when gavage was used which also results in a slower awakening and requires more of an effort on the part of the patient.

We are working in close cooperation with other hospitals in studies of terminations of insulin coma with Glucagon i.m. and several of us use similar observation sheets so that after a time we should be able to collect a great deal of comparable information.

All other hospitals in the project confirm that Glucagon is effective in termination of insulin coma and the State Hospital at Augusta, Maine, also confirmed that they found the combination of adrenalin-thiamine effective.

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Symposium on Hypnosis

CLINICAL HYPNOSIS
Conrad M. Ayres

HYPNOTIC AGE REGRESSION
Milton V. Kline

Clinical Hypnosis

History, Technique, and Characteristics

CONRAD M. AYRES, M.D.*

This introductory outline of the history, technique, and characteristics of the trance is intended for the postgraduate student of medicine or clinical psychology. Hypnosis, or the trance state, is an expression of a natural instinct of life: the return to a state of calm, peace, and relaxation.

The hypnotic trance is a state of narrowed consciousness, mental and physical relaxation, selective hypersuggestibility, and heightened powers of access to unconscious memories.

The history of clinical hypnosis reflects the changed concepts of psychopathology during the past two centuries. Originally, hypnosis found its application in psychotherapy for direct suggestion for the disappearance of symptoms (Mesmer,[1] Braid,[2] Charcot,[3] Liébault,[4] Bernheim[5]). It was then used in conjunction with the cathartic method of psychotherapy in which the patient re-experiences traumatic events underlying his neurosis (Breuer,[6] Janet,[7] Freud[8]). The present trend in clinical hypnosis is to use trance while applying psychodynamic concepts, that is, helping the patient to integrate the abreacted experience into the total personality through emotional insight, so that the original trauma no longer threatens him (Schilder,[9] Erickson,[10] Wolberg,[11] Brenman and Gill,[12] Kubie,[13] Schneck,[14] Spiegel,[15] and others).

There is as yet no scientific basis for determining what makes a patient susceptible to trance, but it is generally agreed that very severe degrees of mental disability preclude the induction of trance and that susceptibility to hypnosis is greatest in subjects under 21 years of age. Preliminary research by this author[16] with nonpsychiatric subjects points to a genetic element in the degree of susceptibility to trance.

During the initial interview, a preparatory period of reassurance and clarification concerning hypnosis is required. The various methods of trance induction are based on the principles of excluding influences which might interfere with the patient's relaxation, and of narrowing the avenues of the patient's sensory intake and motor output.

The method of induction used by this author consists of asking the patient to focus his gaze upon a fixed shiny object or upon the eye of the therapist. The therapist then gives relaxing suggestions in a monotone and requests patient to close his eyes as soon as vision becomes blurred from the approach of the object or of the therapist's eye. The patient is then requested to hyperventilate (breathe deeply); usually he rapidly lapses into a trance.

Three levels or stages of trance are recognized: light (hypnoidal or induction), medium or intermediate, and deep or somnambulistic. The characteristics of the light and medium stages of trance overlap and fluctuate. They vary chiefly in the intensity of their manifestations, which consist essentially of relaxation, drowsiness, heaviness of limbs and eyelids, and, by specific suggestion, the phenomena of motor automatism, paralyses, anesthesia, paresthesias, positive hallucinations, dreams, and hypermnesia. The characteristics of the deep level of trance are an intensification of those of the medium level, with the additional phenomena of age regression, "negative" hallucinations (total disregard of extraneous sounds and influences or selective blindness to objects or individuals), and posthypnotic amnesia of the trance situation, with ability, however, to recall it in later episodes of trance.

Posthypnotic suggestions are directions given to a subject in trance for his "compulsive" performance or inhibition, after termination of the current trance state. A special form of posthypnotic suggestion aims at self-hypnosis. This is a method of trance induction by self-suggestion, with or without the aid of a maneuver (e.g., hand rubbing or twirling) agreed upon during the trance state in which this form of self-suggestion was acquired. Group hypnosis, namely psychotherapy of hypnotized patients in groups, is a form of clinical hypnosis used in order to foster social interaction and integration.

The termination of a trance must be executed thoroughly but gently. The patient should receive suggestions that he will emerge from hypnosis physically and mentally relaxed, with a feeling of well-being. Also, he must be given suggestions that unqualified individuals will not be able to induce hypnosis in him.

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*Supervising Psychiatrist, N. Y. State Department of Mental Hygiene.

Discussion

Hypnosis enables a subject undergoing psychological treatment to gain access to dynamic mechanisms of his behavior in a more direct way than is generally possible in other forms of psychological treatment. In addition, the trance state, through mental and physical relaxation, enhances the subject's natural powers of recovery.

Claims that hypnosis may cause weakening of the will, over-dependency, or inappropriate removal of symptoms of organic illnesses are unfounded where psychotherapists skilled in the use of clinical hypnosis are concerned.

During the process of induction, some subjects display uncontrollable laughter or crying, feelings of sexual excitation, or other emotional outbursts caused by abrupt lifting of repression or of other ego defensive or adaptive mechanisms. These reactions occur in less than one per cent of subjects (usually hysterical individuals), and are readily overcome by skillful application, under hypnosis, of psychodynamic or suggestive forms of psychotherapy (Weitzenhoffer[17]).

Hypnosis may be dangerous when practiced for purposes of entertainment, especially when the hypnotized subject is made to act out some foolish comedy. Stage hypnosis should be outlawed for the protection of subjects of this practice and for the progress of the science of hypnosis. Physicians and psychologists without training in the field should refrain from using hypnosis without expert supervision.

Hypnosis is a safe and valuable psychiatric tool. Hazards attributed to hypnosis are the consequence of lack of competence or ethics of individuals misusing hypnosis, rather than of hypnosis *per se*.

Conclusion

The state of trance is a return to a basic level of behavior rather than regression to a narcissistic stage of development (Schilder[9]).

Psychotherapists using hypnosis must approach each patient with readiness to understand his unique needs and strivings, to discover the psychological conflicts at the basis of the patient's fears or symptoms and to treat the underlying causes by means of suggestion and development of insight. Such treatment, of course, requires a thorough knowledge of the psychodynamics of mental illness.

The hypnotic rapport must be implemented by the therapeutic relationship. Eventually every patient must learn to function without the supportive crutch of hypnosis. Only a strong sense of reality, independent of the use of hypnosis or self-hypnosis, can bring about the necessary integration of the personality and the complete emotional freedom essential for satisfactory social adjustment and valuable creative achievements (Schilder[9]).

2501 Morris Avenue, New York 68, N. Y.

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Hypnotic Age Regression

(Some Dynamic Considerations in Relation to Its Validity as a Research Technique)

MILTON V. KLINE, ED.D.

Recent publications by Reiff and Scheerer (1959), Yates (1960) and Sutcliffe (1960) constituted meaningful studies into the nature of hypnotic age regression with particular respect to the problem of its effect upon memory and levels of mental functioning. These studies continue the investigations of earlier workers into the validity and nature of hypnotic age regression. Scientific opinion continues to be divided as to the validity of this phenomenon when validity becomes equated with exacting chronological criteria.

In a number of previous publications (Kline 1958, 1959, 1960) the writer has stressed the point that hypnotic age regression as an induced behavioral mechanism cannot conceptually be separated from other major hypnotically induced responses such as hypnotic anesthesia, paralysis, hallucinations and various other alterations in sensory and motor phenomena.

Chronological validity is a questionable criterion for the nature of age regression inasmuch as the genuineness of age regression appears to be more in the meaningfulness and reality of the experience to the subject. As pointed out by Schneck (1959) dynamic age regression, particularly as experienced in a psychotherapeutic seting has a particular meaning for the patient and often represents a fusion of material from earlier recollected experience interpreted within the framework of contemporary attitudes, feelings and conflicts.

In this sense, our investigations with hypnotic age regression and other aspects of hypnotic behavior over a period of ten years continues to emphasize the role of transference in this prenomenon of hypnotic behavior. In our opinion the hypnotic transference, a subject of considerable interest in itself, plays a major role in structuring the "outline" age regression, and influences the forms through which it may be experienced. Along with other investigators, we feel that the development of a hypnotic relationship which will permit alteration in the organization of behavior on a "genuine" level requires the utilization of extended periods of time, usually *far beyond* that which is reported in most experimental investigation. Also required is the construction of a basis for an *intensification* of the hypnotic relationship.

For this reason, studies of a clinical nature, usually undertaken within the framework of a treatment setting utilize a level of transference involvement (or hypnotic relationship) which is more regressive in nature (topologically). Extended use of the hypnotic relationship in a non-treatment experimental setting can duplicate such a transference but it will require *emotional involvement* between the hypnotist and the subject equivalent to that which develops between the hypnotherapist and his patient. For this reason, we feel that a great deal of experimental hypnosis is carried on in the folds of a hypnotic transference which for the greater part is structured by the more guarded, vigilant defenses of the waking relationship and results in a greater preponderance of "role playing."

One phase of our continuing studies of hypnotic age regression has employed the use of a Reid Polygraph. Popularly known as the lie detector, the Reid Polygraph is a pneumatically operated mechanical recorder of changes in blood pressure, pulse and respiration supplemented with a unit for recording the GSR (Psychogalvanic Skin Reflex). The polygraph utilized in this investigation also has one additional unit which permitted a recording of muscular activity, particularly muscular pressure exhibited by the subject's forearms, thighs and feet. It was used as a means of measuring emotional response to perceptual alteration and distortion, one evidence of the degree of acceptance or recognition of hypnotically induced states and in this particular instance of age regression.

The examining procedure, both with patients and experimental subjects, involved obtaining characteristic resting patterns both in the waking and hypnotic state (which were not at all different) and using this as the basic criteria against which to compare alterations which appeared in connection with perceptual changes hypnotically produced.

Following are the most striking results, although they reflect only part of the data obtained in this aspect of the investigations:

1. Subjects in age regression examined by the polygraph revealed no evidence of "deception" or its equivalent aspects of lying or simulating

From Institute for Research in Hypnosis.

when questioned rigorously as to the reality of the regressed state.

2. The same subjects nevertheless do, in waking and hypnotic states, show definite evidence of deception or lying when confronted with material that they have either been instructed to or have spontaneously denied. Hypnosis itself does not permit a subject to lie in connection with material which he is consciously aware of as being untrue without showing marked changes in the polygraph recording.

3. Within the regressed state intensive attempts to confront subjects with logical and empirical evidence of their actual chronological status failed to alter polygraph tracings.

The polygraph data suggest that from a perceptual point of view, when a subject is in regression and denies material apart from the regression with respect to his self image, his chronological status and his sense of being, that the involvement in this experience is for him real and does not constitute a degree of deception, role-playing or simulation that would go with a degree of more voluntary behavior. In this respect the evidence is that age regression, like many other forms of regressive phenomena, involves essentially an involuntary process for the subject and constitutes perceptual reality for him.

Other techniques used to evaluate aspects of ego functioning within the regression included Rorschach testing and the Watson-Glaser test of critical thinking as well as intelligence tests and specifically designed learning tasks. The following results were obtained:

In age regression, reality appraisal as it exists in the waking state is temporarily disrupted. Associative links with temporal, sensory and motor cues are either dissociated or so effectively blocked or masked as to permit the emergence of reality appraisal on a newly structured hypnotic basis which is relatively uninfluenced by the externalized perceptions of either the waking or the chronological state within hypnosis. Subjects in age regression believe in the essential nature of the hypnotically induced reality, not through suggestion, but through the natural utilization of more primitive mechanisms of reality appraisal. These are essentially the regressive structures of cognition and the internalized process of perception which may be described under a variety of headings ranging from dissociation and subliminal, to infantile and dependent.

The interpretation of such a process must await a more thorough measuring of its appropriate role in the hierarchy of behavioral organizing process. Although there still remains a considerable amount of work in dealing with the data obtained in this investigation of age regression, it is possible, on the basis of data thus far available, to conceptualize some of the results.

In the form envisioned here, hypnotic age regression, when validly obtained, constitutes a distinctive topological regression in ego functioning which, to the degree that it involves alternating levels of "self exclusion," is *psychodynamically* similar to sleep. The long standing controversy over the relationship between sleep and hypnosis has perhaps been distorted by an over-emphasis upon physiological criteria. For if psychodynamic factors relating to ego functions of self exclusion, vigilance and reality appraisal are utilized, we can see that in certain phases of sleep (lighter) there occur many of the alterations in perception that also occur with somewhat greater vividness in hypnosis.

Where reality determining mechanisms remain primarily linked up with waking levels of ego vigilance and personality mechanisms, hypnotic behavior will for the greater part be on a role playing basis—as it is in waking relationships. With the development of the regressive transference (not necessarily passive-dependent) characteristic of hypnosis when there has been created the basis for intensified interaction on an emotional level between hypnotist and subject, there emerges a more open and less guarded system of reality appraisal. As in sleep, this state may develop either spontaneously or through psychological manipulation into creative experience involving altered elements of memory, time, age and self-expression.

Such experiences, like dreams, hallucinations and the emergence of "ideas" may have varying degrees of "externalized" validity but high degrees of "internalized" validity when determined by criteria of meaning and value to the individual.

It is our feeling that the nature of hypnotic age regression with respect to its validity is essentially the same as the nature of all induced hypnotic behavior. Validity must be interpreted in relation to meaningfulness and the effect of the induced behaviorism upon the individual subject and his level of psychological functioning.

The nature of the *hypnotic relationship* rather than so-called levels of depth as recorded on classical scales of hypnotic response become the real determinants of hypnotic depth and the vital structure in the nature of what emerges through hypnosis. For this reason, it would seem that the *limited emotional involvement* which charac-

terizes a majority of experimental hypnotic relationships constitutes a definitive and significant variation from the hypnotic relationship typical of psychotherapeutic involvement and those experimental relationships which parallel clinical involvement.

In a forthcoming paper, the writer describes a technique utilizing an auditory feedback mechanism which has proven useful in measuring the degree of "perceptual depth" in the hypnotic relationship. Though on a psychophysiological level and devoid of descriptive qualities of the transference relationship, it appears to indicate that type of detachment which gives rise to the degree of "self exclusion" necessary for the production of hypnotically induced behavior on a valid level.

The degree to which psychological reactions expressed through hypnosis may assume the type of validity outlined in this paper is illustrated by the following case material:

A forty-six year old research biochemist was in hypnoanalysis because of frustrating meagerness in his professional productivity despite an extraordinarily high degree of competence and intelligence. He found it very difficult to organize his research data or to integrate it with contemporary work.

During one phase of therapy, the patient spontaneously "regressed" back to his first year as a graduate student when he was twenty-three years old. He described himself as being in the office of his advisor. The conversation which he "reported" involved a strong criticism of his work by his professor with the indication that he was not sufficiently interested in chemistry to be successful at it. The patient then acted out a scene in which he struck his professor and then proceeded to wreck the office, finally setting fire to the room.

Following this hypnotic experience, the patient indicated that though the "regressed" experience seemed frightfully "real" there had never been any violence of the type reported.

Shortly afterwards the patient had a dream about his former professor and advisor, and visualized in the dream, a reprint of a paper written by his professor. The dream so intrigued the patient that he went to the library the next morning and found the reference which the dream had accurately recalled.

Upon reading the paper, he was struck by the fact that his research for the past five years had been in an area of biochemistry closely linked to a series of experiments summarized in the paper. With the material reported in this paper, published some twenty-four years earlier, the patient was able to reorient his thinking. In a few months this led to a number of important scientific papers. These were his first publications in six years!

Subsequent therapy developed the nature of the intense, long repressed hostility toward his former teacher which contained with it a major blocking in his professional output. In turn, this clarified his relationship with his father, an eminent physician who had been extremely critical of his son's progress through secondary school and college, culminating in the attitude often expressed openly, "You are not good enough to be a doctor"!

Like much other human data that emerges through hypnosis, the departure from the stereotyped role playing structured by the "suggestion" of the hypnotist, is determined by the nature and meaning of the hypnotic transference. The motivation and source of stimulation for self-expression must be guided by feelings and values which are meaningful to the subject.

Summary

Experimental research with hypnosis differs very often from clinical research to the degree that an *intensified transference relationship* is developed. Careful attention to this element and its *constructive elucidation in experimental work* may clarify many of the apparent controversial results with respect to age regression and other hypnotic phenomena. Beyond this, such investigations may lead to a more systematic understanding of the dynamics of hypnosis and enhance its value as both an investigative and therapeutic modality.

345 W. 58th Street, New York, N. Y.

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Symposium on Psychiatric Rehabilitation

JOB PLACEMENT OF EX-MENTAL PATIENTS
Janet I. Pinner

REHABILITATION OF POST-PSYCHOTIC PATIENTS BY INDUSTRIAL WORKSHOP
Bertram J. Black

MOTIVATION FOR WORK IN PSYCHIATRIC REHABILITATION
George W. Brooks

SOME PROBLEMS OF RESEARCH IN PSYCHIATRIC REHABILITATION
David Landy

DYNAMIC OCCUPATIONAL THERAPY
H. Azima

PSYCHOPHARMACOLOGY IN REHABILITATION OF THE CHRONIC PSYCHOTIC
Sidney Merlis

Job Placement of Ex-Mental Patients

JANET I. PINNER

There are several facets to the subject of job placement of ex-mental patients in industry—how the Employment Service places ex-mental patients, what our results have been, our *successes*, our *failures* and the reasons for these failures in job placement of this group. I have decided to write about our failures and problems because psychiatry is in a position to take some positive measures to reduce our number of failures. For too long a time, we have hidden behind the rationalization that all our problems center around employers not hiring the ex-mental patient because "they are afraid of what his actions on the job will be."

Not too long ago, the Massachusetts Association of Mental Health* did an excellent study covering 200 employers within the greater Boston labor market. This study was to determine the nature of employer receptivity to the hiring of ex-mental hospital patients and its significance and implications in the rehabilitation process. Their findings showed that employers generally have given little thought to the problem of mental illness: for most of them it was outside the range of their experience and concern. The absence of first-hand experience among employers with mental illness was especially surprising. The report goes on to say that the employer, of course, needs education and that this education could best be done through the maintenance of a high level of employment which perhaps limits their selection of new employees and compels them to give consideration primarily to those personal factors directly related to job performance. These over-all economic conditions are beyond the control of the rehabilitation worker or the psychiatrist. However, *if* we fulfill our responsibility to the patient, *if* we prepare him adequately for employment and for living in the community and *if* we provide him with the required help after discharge, he will then be afforded his greatest opportunity to find and hold a suitable job.

For those ex-mental patients unable to meet the rigors of regular employment, either permanently or temporarily, rehabilitation personnel should try to develop facilities which provide varying grades of sheltered work. In essence, what this report has pointed out is that more attention should be shifted to the area in which we can hope to be most effective—*the area of the patient's needs rather than the area of employers' attitudes.*

Our experience in placing ex-mental patients agrees with this finding. The New York State Employment Service interviews about 400 ex-mental patients every week in its local employment offices throughout the state. We have been able to place about one-third of the group coming to us for placement help. We have experienced little difficulty in placing some of these people *provided* they have something to offer the employer in the way of skills, experience and work habits. The fact that we are able to place one out of three might sound as though there is no problem. However, we have found that some of these placements do not last and that many times we have to make two or three placements of the same individual before we find a job suitable for him. In addition, we worry about the two out of the three that have not been placed. Why is it we cannot find jobs for them? And why do some of our placements fail?

There are two types of ex-mental hospital patients applying to us for placement service. We have the person who has a home and family to return to and who when applying to our local office is able to successfully conceal from the interviewer that he has been in a mental hospital. This man believes that it would be harmful to mention his hospitalization and, as far as he is concerned, he is able to handle the situation. In about four cases out of five, he is able to compete with the other applicants for employment and is able to obtain a job through his own efforts or through friends or relatives or through the help of the Employment Service. This man may have problems but they apparently are not in the vocational area and he is able to present himself as a good employment prospect. This type does not constitute a problem group in the Employment Service.

The group that I am concerned about are those who without any prior conditioning come to us directly from the hospital to take their place in the community. Prior conditioning is a primary need for this group. These are the people, who even without an emotional disability, have very little in the way of skills, potentials or aptitudes

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From New York State Employment Service, Selective Placement Service.

*Rehabilitation of the Mentally Ill, American Association for the Advancement of Science, Washington, D.C.

to offer an employer. In addition to this, their behavior pattern is such that they may be unable to submit to authority or get along with coworkers. In addition, their motivation for work is poor. This is the group that come to us asking for help in securing jobs and for whom we have little success in finding suitable employment. They are so fearful of failure that after we have spent considerable time in arranging for a chance to work they will fail to show at the job, or if they report will quit at the end of a half or full day on some flimsy excuse.

Where does the fault lie? With the patient? With the hospital? With the Employment Service? With the employer? We can't put the blame or responsibility on one without involving all.

For instance, we talk a great deal about rehabilitation in mental hospitals and when we analyze what we mean by this term we find that it relates mostly to the therapeutic processes with little or no emphasis on the vocational aspects of vocational training or placement. Too often, the responsibility for vocational evaluation and training is shunted from one governmental department to another. Merely designating one department as having responsibility without providing adequate financing for staffing is not helpful. As far as I am concerned, and I think this is true of most of the people in the field, we do not care *who* gives the service *provided* that *it is* being *given* to the patients who need it. In the State of New York, our thinking vacillates as to where the responsibility for vocational rehabilitation belongs. At present, the Division of Vocational Rehabilitation is responsible for this function in the State mental hospitals. However, their funds are sadly insufficient for adequate staff coverage. The net result is that state-wise, we are giving very little recognition or service to the vocational needs of patients while they are in the hospital.

The New York State Department of Mental Hygiene several years ago conducted a demonstration whereby they hired a qualified psychiatric employment specialist whose job was twofold—firstly, he worked with the Brooklyn Aftercare Clinic in the day hospital preparing patients for referral to either the Division of Vocational Rehabilitation or to the State Employment Service. Secondly, he worked with the Brooklyn State Hospital in screening those patients who were ready for job referral. There was much bewilderment when he first appeared at the hospital both from the professional hospital staff and from the Division of Vocational Rehabilitation staff in terms of what his contribution could be to the team's work. After a short time, however, it became noticeable that he was clarifying in the minds of the professional staff at the hospital and at the clinic what industry means by the terms "employability" and "placeability" and working out vocational objectives. This was greatly needed as many of the professional staff in the hospitals have not had recent work experience in competitive industry. Time marches on and industrial methods change considerably. Industry has undergone almost a total revolution within the past decade.

From the Employment Service point of view, this was an excellent demonstration in that we felt the referrals from the hospital were well thought out and well documented. Furthermore, the hospital reports assisted us by pointing out the kinds of jobs we should search for in attempting to place the ex-patient. The relationship developed between our Selective Placement rehabilitation staff and the psychiatric employment specialist was that of complete trust with a recognition of each other's skill. We no longer had to clear with the hospital in terms of whether information should be given to us and if so what kind, etc., etc. He knew our wants and was able to communicate the psychiatrist's terminology to us in lay language which we could understand. However, when this demonstration was ended and although everybody agreed that it was worthwhile, the function of vocational rehabilitation was given to the New York State Division of Vocational Rehabilitation, and the New York State Employment Service was expected to continue job placement. I use this as an illustration to show that an attempt was made which proved successful and yet so little appreciation and publicity was given to this project that it died at the first budget cut.

This, I think, is indicative of the thinking in the mental hospitals toward vocational rehabilitation. Too often, it is thought of in terms of someone else's business and not as part and parcel of the rehabilitation process. We know that we cannot release some patients into the community without prior counseling and preparation for employment and expect them to be able to earn their own living. We know, too, that some patients need a work tryout (or trial period) and evaluation in a sheltered situation prior to attempting employment in industry. This is not revolutionary thinking. It is based on experience. For years we have been working with the Veterans Administration Hospitals and have been quite successful in placing some of

their people who had been employed in their "member employee program" as part of their hospital treatment. This is the program whereby the patient is actually hired by the hospital while still confined and works in a hospital department for a certain number of days or hours as specified by the psychiatrist. When he has proven himself in this employment, he is considered for release and is referred to the Employment Service. This procedure accomplishes three things: 1) it hardens the patient for employment and gives the Employment Service knowledge of how this patient has reacted in a work situation. We are then in a position to do a better selective placement job; 2) it gives the patient confidence since he has been in a working situation for which he has received pay and, therefore, is not too fearful of his first contact in the outside world; 3) it helps fill some of the staff openings in the hospital which need personnel. I cannot understand why other mental hospitals have never adopted this technique in whole or in part.

Another asset of the Veterans Administration Hospitals is the availability of counseling psychologist with a Ph.D. degree. They handle patients on a casework basis and work with those patients who have vocational problems. When the veteran is ready for discharge, their evaluation of what the patient is able to do is given to us for placement purposes. However, they can handle only a fraction of the veteran load, but those they do serve are proof that the counselors' efforts pay off in terms of determining the man's ability to take his place in society.

The sheltered workshop is currently considered the answer to our problems. However, here too, we run into obstacles. Some workshops in the mental hospitals are being run either as therapy shops or as diversional occupational therapy shops with little or no evaluation being done as to the patient's skills or potentialities for industry. The mere setting up of a shop in a hospital does not necessarily mean that you are preparing the person to take his place in industry. This can only be done if qualified personnel are available to operate the shop; if the objectives of the shop have been carefully spelled out; if the person selected for the shop meets certain established criteria, and finally if there is follow-up of what happens to the patient after he leaves the shop. The tempo of the shop must simulate industry and not an occupational therapy department.

There are others who suggest that the answer to the problem is for sheltered workshop in the community to extend its services to the ex-mental patient. This is just plain wishful thinking. If you think employer attitudes are poor toward the mentally impaired, you should hear some of our professional rehabilitation workers give reasons why this group should not be in the same shops as the physically impaired. Employers aren't the only ones in need of education! The end result has been that throughout the State of New York, which has long been an acknowledged leader in the sheltered workshop movement, there are few who will accept an ex-mental patient without a physical disability for either evaluation or hardening. We know that some studies have shown one out of five patients need this help, yet little is being done to provide this service.

Another interesting movement in the field has been the work done at Fountain House,* a voluntary agency in New York City, originally set up to provide social and recreational programs for persons discharged from mental hospitals. They have inaugurated a unique program by arranging with several private employers to accept carefully selected persons for a two-month try-out period. The employer is given all necessary information about the applicant. He also knows he will have someone new every two months. The applicant knows that it is not a permanent job, but an opportunity to try himself out and a means whereby his work potentials can be evaluated. After the two-month trial period, if he seems ready for a job, referral is made by Fountain House to a selective placement interviewer in the Employment Service. While this project is still very new and deals with a small group numerically, it demonstrates that there are new methods and new techniques.

We have come a long way in the job placement of this group in two decades. We probably will not have all the answers in our generation, but we feel confident that, at least, we are thinking about the problem and making attempts to solve it. We in the Employment Service feel strongly that this is a group of people who cannot be placed in industry by merely appealing to employers by means of snappy slogans such as "Hire the NP's." Each worker must be handled on an individual basis in order to be properly placed.

*Cooperation of New York State Employment Service and Mental Health Facilities, Hourwich, Olga and Altman, Anne—Employment Security Review, September, 1960.

Rehabilitation of Post-Psychotic Patients by Industrial Workshop

BERTRAM J. BLACK, M.S.W.

Over the past seven years, Altro Health and Rehabilitation Services has been active in the rehabilitation of patients discharged from mental hospitals. Although rehabilitation programs for the mentally ill have existed in other parts of the world for many years, Altro's program is among the first in the United States. It is also one of the first to make use of the sheltered workshop setting as a controlled industrial transitional environment for the return of this group of people to industry and commerce. In these seven years, some 250 post-psychotic patients have been served by Altro Work Shops and its rehabilitation services, starting with a small group of some half-dozen patients in the first year and building up slowly to the point that we now have some 35 to 40 psychiatric patients under care at Altro Work Shops at any one time, and some 150 such patients in the active rehabilitation load.

The Altro program began as a service to the patients discharged from tuberculosis sanatoria some 48 years ago. In 1943 the rehabilitation of the cardiac was added to the program and, thus, when the plan was evolved for rehabilitation of the post-mentally ill, Altro already had a body of experience with chronic illness where the danger of relapse or exacerbation is always present, and where it was felt that the emotional characteristics of these ailments might not be too different from those to be faced in the rehabilitation of the mentally ill.

The detail of Altro's program has been described in a number of presentations and publications over the past few years. Rather than take time to repeat this detail, I will only say that we offer the complete array of professional services common to a modern-day rehabilitation center specializing in the relapsing, exacerbating, chronic illnesses. In addition, we have available a large and well-equipped sheltered workshop, designed and operated as a factory in the open, competitive market, and which supplies a relatively normal work setting for the rehabilitation of patients.

Altro Work Shop, Inc., is three businesses rolled into one. Its largest and oldest enterprise is a garment factory, manufacturing light washable cotton garments for the open, competitive market. The patients who work there are paid at the going industrial rate for their production. Housed in the same factory building is also a mechanical division, consisting of a small well-equipped machine shop and mechanical bench assembly in simple mechanics and in electronics. Our third business enterprise is the Altro Clerical Service Bureau, which offers a lettershop serving other businesses and industries and, at the same time, has a statistical-clerical service prepared to undertake the clerical part of research and other statistical analytical operations. On any one day, approximately 140 patients are employed in garment operations, about 20 in the mechanical division and about 20 in the clerical service bureau.

I should like to discuss some of the principles, experiences and ideas that have come to us out of operating a sheltered work program for the post-psychotic. First of all, what kinds of patients are we serving and what are we trying to do for them? It is in a spirit of scientific approach that we have restricted our patient population to those who have been discharged from mental hospitals rather than open our doors, as has often been suggested, to the entire array of population labeled as suffering from psychiatric disorders. Even this restriction, however, has not left us with as homogeneous a population so far as illness is concerned as has been true of our tuberculous or cardiac patients. The diagnostic label of psychotic or even of schizophrenia shows a considerable variation in degree of pathological severity. There is no guarantee that the schizophrenic so labeled by one hospital corresponds to the similar classification of another. Nonetheless, in speaking of our patient population, we at least have the advantage over many other rehabilitation and treatment services in that our patient load can be described so as to have meaning to those familiar with the type of patients being released from our public and private mental hospitals.

Celia Benney and Shirley Waltzer have described Altro's population as:

"Anxious, ambivalent, withdrawn, they are eternally caught in conflict between their infantile emo-

From Altro Health and Rehabilitation Service, Inc.

tional needs and the expectations of society. Beginning with relatively weak egos (perhaps at times on a constitutional basis) and battered by rejection by significant people, they are forever seeking the unattainable. Their needs, frequently on every level and in every sphere, are great."

What are we trying to do for these patients? We see the Workshop as an intermediary station between the hospital atmosphere and the real world. We see it as offering the patient a life space, a conditioned environment, a milieu, in which it may be possible for him to learn through trial and error, in an actual life situation, the habits and the skills of performing work without the immediate dire consequences of error which exist in the real world. In rehabilitation terms, our setting can provide for the patient the opportunities for work evaluation, testing out skills, developing additional work skills and habits.

Putting it another way, the Workshop offers an opportunity to build upon what health there is left in the patient's ego, and to develop such additional ego strengths as will make it possible for him to become a stable working member of society.

With this in mind, the question then arises as to what we consider work? Certain principles built into the Altro program for our earlier illness groups apply equally well to the post-psychotic. It is our belief that in returning an individual to the world of work, he must be returned as rapidly as possible to as much as what is normalcy as he can absorb or accept. For these reasons, the atmosphere in which he is placed must be as close to that of the real world of work as is possible to achieve. We believe in a work atmosphere with real work for which there is payment on the basis of productivity in conformance with the highest standards paid in local industry. We believe in supervision being from people skilled in the trade or the vocation which they represent. We believe in the type of equipment that is normal to the industry producing the product, and we believe that quality of product and of performance are as important in the sheltered work setting as they are in the industrial plant out to make a profit. At the same time, we recognize that we are dealing with an employee force which has problems of its own and characteristics that are different from those of the normal labor force. We must be prepared, therefore, with the necessary working conditions, and supervisory personnel understanding of the strengths and weaknesses of this special labor force, so that we do not violate their health condition nor undercut the efforts of the professional rehabilitation staff in their aim of increasing the ability of each of their patients.

This rehabilitation personnel, or what we have called the ring of protective services around the workshop, is an absolute necessity to the success of rehabilitation of this sort. Vocational planning and the work environment alone, we are thoroughly convinced, would not work without the array of professional disciplines and the armamentarium of modern medical advances. There is a constant interweaving and cooperation between the rehabilitation services and the sheltered workshop, and this must be done in such a way that the real world of work is not transformed into an exercise in work therapy or become what is today more readily recognized as a type of day hospital. On the other hand, so much stress must not be placed upon the work atmosphere apart from the professional services, that the workshop becomes, in essence, a setting for permanent sheltered employment of people instead of emphasizing their transition to the normal world of work.

I am often asked why, if there is the necessity for close working together of the sheltered workshop and the professional staff of psychiatrists, psychologists, vocational counselors, social workers and nurses, and the like, it would not be wisest or more convenient to have the sheltered work setting within the structure of the hospital where the array of professional services is always available. I believe that such a question loses sight of a most important reason for the existence of the transitional sheltered workshop, and poses a conflict in professional philosophy where none really should exist. Recent studies by Olshansky and his colleagues in Massachusetts, and by Elsie Kris in New York City, have shown that the vast majority of patients discharged from mental hospitals, probably 70 to 80 per cent, find it possible to return to the employment market and the world of work without requiring much in the way of special post-hospital services. It is likely that even with the development of better therapeutic services within the hospital before discharge, and with greater emphasis upon more adequate vocational preparation, the 20 to 30 per cent who now require some transitional post-hospital assist might be reduced to 10 or 15 per cent. This is still a large number of people and the existing resources for them would have their hands full were they all referred for service. Parenthetically, as it stands now, so limited are most in-hospital services and programs that most of this group come out of

the hospital unprepared for the work-a-day world and with few facilities available to them. A fairly substantial number of those who finally make the grade in the world of work flounder or fail.

The concept of rehabilitation planning is for the provision of services from the onset of illness, or at least the onset of treatment, until the return of the patient to normal society and functioning at the highest capacity that his handicap will allow. Along with the open ward program, the day hospital, the night hospital, more adequate occupational therapy, better vocational counseling, more adequate use of chemotherapy, better psychotherapeutic services of all sorts, the sheltered workshop could become a dynamic and valid part of the treatment armamentarium of the large mental hospital.

It should be kept in mind, however, that such a sheltered work environment, within the walls of the mental hospital, is quite a different resource than is the sheltered workshop in the community. The latter is a business enterprise, part of the socio-cultural milieu of normal society; the former is a facsimile of industry, designed to serve a particular therapeutic purpose. There is more of a guarantee that the patient who can perform adequately in the community program will perform adequately on the job in industry. One is not a substitute for the other; in fact, the existence of a well-run sheltered work program within the hospital increases the likelihood of referral to the sheltered work setting in the community. The community workshop is a natural transition for the 10 to 15 per cent of the patients who show promise within the hospital but who are so fragile or have so many additional social and psychological problems facing them in the community that their attempts to work are likely to be fraught with disaster before they can even get off the ground.

It is interesting to note that in the history of rehabilitation of the tuberculous, whenever good rehabilitation programs were built into the sanatoria the number of patients referred for community-based rehabilitation increased from that institution. The placing of services at any point on the spectrum of rehabilitation does not eliminate the value of placing services at other points. In fact, the more lines in the spectrum are activated, the brighter are the colors, the clearer the distinctions between them the less concerned we become with the areas and shades of overlap.

At the 1959 annual meeting of the American Orthopsychiatric Association, Dr. Leopold Bellak and I stressed that rehabilitation be arranged for as early in the patient's stay in the hospital as possible. For that group of patients likely to be referred to the protected industrial workshop in the community, there should be planning that takes place within the hospital and consideration of the patient's assets and liabilities and life situation. We pointed to characteristics of the Altro program which we believe are significant in the operation of any protected industrial workshop for this group of patients. For example, planning for the management of any crisis that might occur while the patient is in the protected work setting depends greatly upon the kind of formulation and understanding of the patient already undertaken in the hospital before discharge. We have pointed out that during the workshop phase of the patient's rehabilitation there are distinct advantages in dealing with transference problems by recognizing the roles which not only the professional staff, but the workshop management and supervisory staff can play. We have pointed to the opportunities within the workshop for the patients to "learn object relations, to acquire frustration tolerance and anxiety tolerance in an environment that is realistic but flexible in its demands." We have given due credit to the great role played by the tranquilizers. If chemotherapeutic means allow a strengthening of the ego by decreasing aggressive or sexual impulses and their ensuant complications and sequelae, and if such strengthening seems vitally necessary to avoid rehospitalization, drugs are obviously a good thing. There is no question, empirically speaking, that a good percentage of patients could not have been kept in the community without drugs.

A well-run rehabilitation enterprise, with psychiatrists, social workers, nurses, psychologists, vocational counselors and factory personnel actively cooperating in behalf of the patient's interest, includes a component that is absolutely necessary to successful rehabilitation. This is what Celia Benney has called "realistic therapeutic optimism." In dealing with the post-psychotic, and particularly with the schizophrenic, there is rarely this optimism. Too frequently patients are referred to us with the notation from the referring hospital or psychiatrist that this is an individual not susceptible to treatment. The attitude seems to be that since he is not able to function adequately as a socially adjusted member of society, but since modern treatment, including chemotherapy, has made it no longer necessary to keep him custodially in the hospital, he be provided with some sort of a

sheltered work setting where he could be protected from the demands of society. We have no desire to see the protected industrial workshop replace the custodial wards of the hospital.

We believe that anyone who has reached such capacity that a qualitative psychiatric judgment of high standard finds him able to return to the community, should be given an opportunity to develop those ego strengths and capacities that make it possible for him to maintain himself at a relatively stable level. Everyday we are surprised at the forward movement made by patients who come to us. While it is too early to measure success rates with the scientific rigor they deserve, our constant follow-up of the patients we have served has shown a 70 per cent "success," as measured by the simple community criterion of whether the individual is maintaining himself in a job, in schooling, or in homemaking.

One of the responsibilities of our program and, in fact, of any post hospital rehabilitation program today, is to learn more about the post-psychotic, what makes him tick, and how he can perform as a useful member of society. We must also learn more about our own management techniques, what are the most valid forms and levels of cooperation between treatment resources, the aftercare clinic, and the rehabilitation services, and what clues there are to helping society itself, and industry in particular, to make productive use of the large numbers of folk in their ranks with lesser or greater chronic mental illness.

As that early physician, Galen, said in 172 A.D., "Employment is nature's best physician and is essential to human happiness." We also believe in today's modern medicine that the physician requires the best that psychiatric treatment and community services can make available to him. As is true in other branches of medicine, in the treatment of the mentally ill and particularly in his rehabilitation, a physician needs an occasional assist from the rest of the rehabilitation team.

Motivation for Work in Psychiatric Rehabilitation

GEORGE W. BROOKS, M.D.

The importance of work therapy in hospital treatment and rehabilitation of mental disorders has been emphasized since the end of the eighteenth century, the modern era of treatment. All the pioneers in humane treatment emphasized useful occupation as essential. Pinel, Tuke, and Rush very strongly recommended active programs of industrial therapy. However, the rationale for this treatment remained vague and superficial throughout nearly two centuries. It often sounded more like rationalization than a rationale. Bond[1] quoted Kirkbride as having said, in 1842, "The value of employment in the treatment of insanity is now so universally conceded that no arguments are required in its favor. Its value cannot be reckoned in dollars and cents. The object is to restore mental health and tranquilize the restlessness and mitigate the sorrows of disease." Discussions of the subject throughout these nearly two centuries have sounded little different and have been on the level of "the Devil finds work for idle hands." Charlotte Schwartz[20] has very adequately summarized this literature and grouped the suggestions as to the value of patient activities under five headings: 1) Improving and increasing the socialization of patients; 2) providing outlets for hostility and aggressions; 3) taking the patient's mind off his problems; 4) improving confidence and training or retraining in skills; 5) binding the patient to the world of reality.

Freud was interested in the meaning of work for the individual. Linn[14] quotes him as having said in 1939, ". . . work has greater effect than any other technique of living in the direction of binding the individual more closely to reality; in his work at least, he is securely attached to a part of reality, the human community." However, Freud contributed little else to our understanding of the significance of work to the human personality. As outlined by Riesman,[18] his own attitude towards work was somewhat Victorian, if not Calvinistic. He seemed to feel it was a necessary evil and to be endured rather than enjoyed. Not until the past few years do we see the beginnings of a deeper interest in the value of work therapy and its meaning to the patients. Despite the fact that work therapy apparently has remained the primary mode of hospital therapy in Europe throughout the last two centuries, as Kalinowsky[11] suggests, its value has apparently seemed so obvious to most workers that their curiosity has not been piqued.

We owe our own interest in this area to Doctor Landy, and to a paper which he delivered in December 1957 at a meeting in Indianapolis.[12] Doctor Landy gave an excellent summary of the literature and emphasized the need for realistic work settings, careful and detailed coordination of work therapy with other aspects of the milieu through effective communication, and inclusion of the patients in the decision-making process.

Denber[3,4] has recently and extensively sought to stimulate interest in the value and meaning of work therapy, particularly as defined by a sheltered workshop within the hospital. He points out the reduction in hospital dependency and the assumption of ego-satisfying roles. His patients also stressed the value of earnings in making them feel independent and that work relieved boredom and took their minds off their troubles. He also emphasized the importance of structured and meaningful object relations in the value of work therapy, especially for schizophrenic patients. This is reminiscent of the object relations therapy of Wittkower and Azima[22] and Semrad and Day.[21]

Peffer[16,17] has been a pioneer in the value of remuneration in hospital labor as a therapeutic technique with mental patients. His member-employee program has long been successful in assisting patients to bridge the gap between hospital and community. He emphasizes strongly the value of money as a motivation in our culture. He notes the need for demanding increasing responsibility in recovering patients.

However, to find more extensive and meaningful analyses of the work situation, we must turn to sources outside the mental hospital setting. Friedmann and Havinghurst[7] made an extensive study on the meaning of work and retirement to different classes of workers and found such gratifications as money, fixed routine to avoid boredom, self-respect, prestige, association with others, purposeful activities, creativity, novel experiences, and service to others to have value for different classes of workers ranging from unskilled to professional.

Perhaps industrial psychology has performed the most extensive research in the area of motivation for work. In a series of classic experi-

From Vermont State Hospital.

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ments, they have long since discounted incentive pay and other more tangible benefits as an effective, long-range motivation force. This work has been summarized excellently by Drucker.[5] He points out that the effective motivating for performance in labor is responsibility, not fear or satisfaction. He outlines four roads to the inducement of responsibility in workers: careful placement, high standards, adequate feedback of information to the worker, and opportunities for participation in management. He emphasizes the significance of the studies demonstrating the importance of maintaining a smooth functioning work team. Most studies demonstrated that maintaining the integrity of the production team is the greatest single factor in maintaining production.

Linn,[13] in summarizing the theory of work therapy, stresses the importance of developing particular skills in the transition from helpless dependency to self-sufficiency in normal personality development and the importance of an occupation in the formation of a mature identity with self-esteem, pride, and a sense of personal accomplishment. He also cited the studies which show that on an average, normal social life tends to develop around group working situations. He suggests the value of work in sublimating instinctual drives through such symbolic activities as skill with a "tool," possessing a large "bank roll," producing a loved object, and resolving guilt towards demanding parent figures. He also suggests some unhealthy motivations for work. There is, for example, the compulsive worker who tends to ward off unacceptable feelings and impulses to which he is unable to adapt by working constantly.

Heider[9] suggests that in comparing one's lot with others, one differentiates between work which is felt as striving for goals that are not one's own and are imposed from above and striving for goals which are personally gratifying. He also suggests that the value we put on our work often depends more on the energy we expend than on what we produce. We feel that the strong should work more, the weak less, for the same reward.

Thus, we see that there is a rapidly accelerating interest and understanding about the motives for work which have developed in very recent years after a prolonged and non-critical recognition of the empirical value of work therapy. Our own experience covers about six years of an intensive vocational rehabilitation program for chronic schizophrenic patients in which we have succeeded in restoring about half of a group of 308 chronic patients to vocational and social self-sufficiency. Our primary research concerns in studying this program have been the delineation of the positive factors which have allowed such a result and the answering of such questions as: Why does a patient work? What does it mean to him? How does it contribute to his recovery? How can the work therapy situation be improved to make it even more effective? Research methods employed were primarily participant observation, phenomenological inquiry, and some historical analysis.

Historical motivation for the work program at our hospital differed little from that at most hospitals. It consisted primarily of a rather complex system of rewards and punishments. Patients who worked were rewarded by free tobacco, a somewhat better diet, and increased privileges plus an occasional party or picnic. Patients who did not work were punished by the withdrawal of these advantages. The entire system worked quite well to maintain a fairly stable labor force; it apparently also assisted in maintaining a stable patient population and differed very little from forced labor programs in other situations in other places. There were, as is common, a number of patients who worked compulsively and in a sense hid from the world behind their jobs. There were occasional sporadic therapeutic benefits usually associated with some close relationship with a work supervisor. There was little movement in the chronic patient population and their lot was considered essentially hopeless.

Since the advent of an intensive social therapy and rehabilitation program six years ago, we have been able to observe the evolution of a far-reaching series of changes in motivation for work. The program was originally designed to enhance formation of stable groups among chronic patients. Patients were kept together in group therapy, group living arrangements, group activities, and, as much as possible, in group work projects. Observation showed that patients who were poorly motivated or not at all motivated for performance in any other kind of setting, frequently became highly motivated in a team setting. They performed well at such tasks as making a float for a parade or booths for a bazaar; writing, producing, and performing a play; preparing, serving, and eating a meal; planning and conducting a lecture series; repairing and redecorating a rehabilitation house, etc. All these remind one of the classic example of the building of the Kiosk at Chestnut Lodge.[10] We thus confirmed for a group of chronic schizophrenic pa-

tients the finding previously reported in industry that the integrity and spirit of a working team markedly affected work performance.

We also detected a rapidly progressive change in the attitude towards work placement both in the rehabilitation service and in the rest of the hospital. The relationship between working in the hospital and placement through vocational rehabilitation efforts apparently became obvious to many patients rather early in the program. Where formerly it had frequently been difficult to find a patient willing to accept a job, patients began to volunteer for work, usually saying to the industrial therapist, "Why don't you find a job for me so I can get on rehab?" Apparently the same type of work done under the same conditions by the same patients had an entirely different value and meaning when it was tied in with potential rehabilitation rather than merely fitting the needs of the institution or the demands of the traditional reward and punishment system.

A series of efforts were made to improve communications regarding work progress. We tried to keep all members of the team, including the patients, informed about the work progress of individuals and the relationship of progress to the vocational planning goals. A series of work progress reports was developed to give reliable information which would be useful in determining readiness for vocational planning and placement. Work supervisors were routinely included in planning and decision-making meetings regarding individual patients. They were also included in meetings concerned with the overall progress and policies of the program.

Placement of patients in hospital industry was continually studied and improved. A close working relationship was established between the industrial therapist and vocational counselors. Vocational preference and aptitude tests were used when indicated. Every attempt was made to make the patient's hospital work experience meaningful in terms of work training and evaluation for eventual vocational rehabilitation placement. The patient's work thus acquired a meaning in terms of realistic goals for the future.

Continuing participant observation and concurrent feedback of information led to the development of new hypotheses and hypothesis-oriented action research. This was controlled and evaluated by participant observation. We were led to the conclusion that a high degree of expectation and of structured responsibility were essential for the achievement of job satisfaction and improved motivation for performance. Work norms were studied and raised for most areas of the hospital, although in some areas where the work week had included about seven 12-hour days, they were reduced. Expectations for performance were formalized after considerable action research and much group discussion. The areas of most significance and highest expectation were initiative, dependability, maintenance of a schedule, learning, attitude toward change, cooperation, group participation, dress and appearance, and attitudes toward authority. Many of the details of the industrial therapy program have previously been reported by Guyette and Deane.[5] These developments growing out of a participant research and social therapy program are highly reminiscent of the findings of Scher[19] in a controlled study of structured versus permissive ward settings.

We attempted to gain some idea of the meaning of the working world of the patients' and the importance of the work experience in the patient's view of his recovery processes. The overall results of this study have been reported elsewhere.[2] Specifically, in regard to work, 32 out of 74 released patients mentioned work or work situations as of importance in their recovery or in the poignant events which constituted a turning point in the progress of their illness. They mentioned them sometimes in such vague terms as making them feel better, more content, or less bored. They also mentioned particular relationships with work supervisors occasionally. A larger number also mentioned the importance of having some money from work on the day placement program. However, they more frequently mentioned a more inclusive concept of the meaning of work through such phrases as "getting back in the groove," "getting oriented," "getting with it," "getting my thoughts off myself," "looking ahead," "clearing up," "things beginning to register," "getting new hope," "catching fire," "like living again," etc.

It would seem, then, that for these patients the world of work represents not only the standard meaning ascribed to it by others, an opportunity for reality binding, but also an opportunity for some transcendence, getting out of themselves and living beyond themselves. In this respect, they also mentioned "deciding to get well" and thus seemed to confirm some of the formulations of Frankl.[6]

Our industrial therapist and work supervisors have become alert to many other aspects of work therapy through their participation in our research. They have observed that many patients

seem to enter into recreational activities with more zest and meaning after achieving a meaningful work experience. In this sense, the patients probably mirror the cultural norm that play should be reserved for those who work effectively.[15]

It has been exciting for our people to observe the transformation that takes place in the working relationships of the same patients doing the same jobs in the same settings for many years when work suddenly becomes imbued with meaning in terms of self-development, self-transcendence, and realistic goals. Work that was formerly a compulsive task to hide behind, an unrewarding, ungratifying, necessary evil in the impoverished economy of the patient community, suddenly became an exciting experience which brought the patient out of himself and eventually out of the hospital; not as a refugee from an irritating round of activities but as a migrant to greener pastures.

In conclusion, we would suggest that adequate motivation for work in psychiatric rehabilitation depends more on an opportunity for meaningful encounters with other workers in a team, the provision of meaning and responsibility in the world of work, and the opportunity for transcendence which this provides than on the more traditional factors of reward and punishment. Apparently the reward and punishment scheme leads to a stable and sterile system of minimal gratification of patients' needs and to chronicity. What seems to be needed for successful rehabilitation is some degree of instability, disequilibrium, and gradually increasing tensions in a structured setting.

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Some Problems of Research in Psychiatric Rehabilitation

DAVID LANDY, PH.D.

Rehabilitation of psychiatric hospitalized patients may be said to commence with the patient's first contacts with lay and professional members of the family and community insofar as these contacts, consciously or unwittingly influence his health and behavior (Landy, 1960). The process becomes intensified when the patient is placed under formal treatment either in the community or in a mental hospital. It continues in the posthospital period ideally until the person has been restored to a relatively adequate and gratifying level of social and personal competence. Through improved techniques in psychotherapy, somatotherapy and social or environmental therapy, the patient's chances of being brought to a condition of readiness for hospital discharge have been augmented dramatically. Increasingly, therefore, attention has become focused on the posthospital phase of rehabilitation. The key problem now is not simply to get the patient out of the hospital, but to enable him to reconstitute his social and personal life-ways in the community.

Among the devices used with increasing frequency as transitional facilities for patients returning to the community are day hospitals, night hospitals, halfway houses, sheltered workshops, expatient clubs and foster home care. For the purposes of this paper it will not be necessary to select a particular one. Let us assume that the administrator of Agency X, a composite type of transitional organization, has decided to find out what his agency has been doing and whether it has been "successful" and has decided to employ a social scientist to design and carry out the research.

Defining the Problem

Frequently in such a situation the administrator feels that he has a crucial problem and wishes he had some answers. This in itself is justification for *wanting* to do the research, but not for actually embarking upon a research project. If the administrator is not able to delineate the problem in clear, researchable terms, it is imperative that the researcher establishes as part of the contract, that the initial stage of the research will be spent in defining the problem in dimensions that lend themselves to rational investigation. To plunge into research without this initial stage of "fact finding," as Flanagan (1959) has termed it, and without learning something of the operation and organization of the agency, is to research in a theoretical vacuum. If no attempt is made to go through the initial exploratory stage and to utilize a theoretical model, then interpretations of findings are apt to be meaningless or unconnected to each other. Even worse, the actual collection of data will be blind, since the directions are unmarked and unknown. I need not belabor the often-expressed fact that research in this field sorely needs better theoretical underpinnings.

Clarification of Assumptions and Goals

An important element in the process of defining the problem to be researched is the clarification of underlying assumptions of the agency and the goals toward which it strives. This is also necessary in order to specify the criteria for measuring rehabilitation success or outcome. Assumptions are not always made explicit, indeed are not always easily recognized. It is possible to tease out some assumptions which appear to be common to all of them, whatever their differences (Landy and Wechsler, 1961):

(1) The provision for continuity of the rehabilitation process. (2) The provision for a "delaying action" which is felt to soften the impact of return to a more socially and psychologically demanding environment than the hospital (the pathway organization is presumed to provide a transitional step, something in between the relatively protected milieu of the hospital and the relatively unprotected one of the community). (3) The provision for socialization or resocialization on a more nearly "normal" or "realistic" basis than that provided in the hospital. (4) Though more protected, the provision, paradoxically, of a more open social system than the hospital; this greater openness of system is assumed not only to encourage interaction with other members of the agency, but to provide greater and quicker access to the general community. (5) The provision of a less professionally oriented organization than the hospital; as a corollary, the members are considered to require less intense supervision than in the hospital. (6) The provision of a further step in the weaning of the patient from dependence that in part is due to his illness, in part to living within a completely sheltered, relatively highly struc-

From the Graduate School of Public Health, University of Pittsburgh.

tured "total institution" (Goffman, 1957). (7) The provision of an intervening status between the patient role and non-patient role, the sick role and well role, the normal and the abnormal, that contains some of the attributes of both while not being sharply defined as either.

Undoubtedly additional common assumptions and value-orientations could be teased out, as well as some which are peculiar to the particular Agency X. The problem for effective research is to have as many assumptions as possible made explicit by the administrators and collaborators with the agency (for example, hospitals and clinics which send discharged patients to Agency X), and then to see to what extent the less clearly recognized or latent assumptions are consonant with the explicit ones. These assumptions are also, to some extent, the *goals* of the agency, but again the goals must themselves be specified. Only a set of goals capable of testable specification can provide the criteria for measuring the degree of success of the agency.

Criteria for Measuring Rehabilitation Success

Criteria for rehabilitative "success" or outcome should not spring from the mind of the researcher; necessarily they must be supplied, and agreed upon beforehand, by the agency. Furthermore, there must be agreement between administrators, clinicians and researchers as to the elements of a successful or unsuccessful rehabilitative condition, as well as the measures to be used to evaluate this condition. Finally, sufficient data must be collected to render judgments that can be subjected to the usual scientific tests of reliability and validity. If any one of these prerequisites is missing, or becomes impossible to fulfill, it is imperative that administrators, clinicians, and researchers should not permit themselves to be deceived into believing that they are actually evaluating the rehabilitative state of the rehabilitatee, and the effectiveness of the agency.

Moreover, it is not enough to achieve consensus within the agency in defining what is to be studied and how it is to be measured. The researcher must also attempt to bring these criteria into line with existing knowledge and experience in the field; that is, while every researcher necessarily resorts to operational definitions in order to be as specific as possible, he cannot take refuge in definitions of aims and criteria of measurement which are almost completely idiosyncratic to one agency or one or two clinicians. If he does feel the necessity to do this, then he must be certain to communicate clear, logical reasons for this choice. He is compelled to have his criteria "make sense" to others in the field generally, else the scientific validity of the research is open to question since the basic requirement of scientific research is that it can be replicated.

Clinicians have wondered, of course, how situations, and individual conditions and life histories can be replicated. This question is not easy to answer. But if the research design is at least set up on the basis of *possible* replication, then hopefully conditions will exist for repeated studies in other settings. Without this prerequisite all research in rehabilitation will necessarily be open to serious question. If clinicians are willing to accept the supposition that drug research on humans can be replicated, then they must also go along with a similar supposition for research on the effects of less tangible—though nonetheless real—treatment modalities, whether psychotherapy, nursing or occupational or work therapy in the hospital, or a halfway house or day hospital. It is not easy to account for all changes that take place in an individual's personal and social behavior, let alone for the psychological or social forces that were responsible for them. But then, neither is it always so simple a task to account for physiological and biochemical changes that take place in the organism being treated with a particular drug. It is simply assumed that the physiological and biochemical balance remains constant, except for the effect of the particular pharmacological agent; I doubt very much, however, whether any physiologist or biochemist or neurologist really believes that in fact the body economy remains docile and static while responding only to the particular experimental agent. The researcher is forced to make assumptions about biological constancy for the purposes of his study; he is also forced to make similar assumptions about psychological or social constancy. If he could not make such assumptions, then there would be little hope for a science or sciences of biology, and similarly, there would be little hope for sciences of personal and social action.

The Need for Controlled Studies

Even if all the prerequisites for setting up criteria for a measure of rehabilitation level or status are fulfilled, so that we may be reasonably certain that we are indeed measuring something that we can with confidence term rehabilitation status, we must fulfill many other requirements in order to evaluate the effectiveness of a rehabilitative agency or agent. The rules for this are no different than those for the evaluation of

any type of treatment, *or for that matter the effect of any presumably independent or experimental variable on any dependent variable.* Clinicians who would fervently agree with this in the case of other types of research, feel somehow that such prerequisites may be bypassed when dealing with the effect of a rehabilitative agency.

Let us start with the premise that we can never know the effects of an agency if we do not also have good reason to know that the modifications which are presumed to have been caused by it could not in fact have been caused by factors other than the independent or experimental variable. This means that we must not only have two groups, one of which (the control group) has not been exposed to the agency's services, but we must also know that the groups are not selected on the basis of characteristics which, we may know by past experience, seem to go along with relatively successful rehabilitation. In other words, the groups must be chosen by some process of randomization, and the randomization sequence must be unstintingly followed, else the whole purpose of the procedure is lost. We must pick the two groups randomly from the same population, and must have good reason to feel that they are relatively evenly matched with regard to major characteristics that might otherwise spell the difference between true and pseudo-effectiveness of the experimental variable. If, between the two groups, there is a statistically significant difference in the dependent variable, we may accept as reasonable the hypothesis that the difference was indeed due to the independent variable, namely, the agency's intervention. If there is either no statistical difference between them, or the control group actually turns out to have a significantly greater degree of the experimental variable, then we may not only assume that the effect on the experimental group is not due to the intervention of the agency, but the possibility may be considered that the agency in fact either is not having the effect it was intended to have, or is having an opposite, and therefore "negative" effect.

However, as I have pointed out elsewhere, it is not easy to carry out a true experimental design since "(1) . . . subjects are human beings and ethical problems are raised regarding the giving or withholding of treatment; (2) . . . few physicians or other practitioners wish to prescribe treatment via a table of random numbers" (Landy, 1959). One possible alternative to randomization for *some* study designs is to match samples, individual by individual. However, "matching designs are not easy to execute since little is known of the variables along which patients should be matched and compared. Classic sociological factors like age, sex and socioeconomic status may not in fact be crucial or significant in studies of pathway agencies; and significant variables have not as yet been clearly identified" (Landy and Wechsler, 1961).

Psychiatrists and social scientists who have attempted rigorously to carry through control studies know how frequently they can be sabotaged by individual practitioners who prefer not to withhold the particular treatment from one of their patients, or contrariwise, not to expose their patients to the experimental variable. Only a high degree of secrecy with regard to identifying the experimental and control subjects will provide protection against biasing of the outcome by overzealous nurses and others paying inordinate attention to the experimental subjects in order to bring about the success of the research and enhance their own status as well.

One type of solution that enables the researcher to dispense with a control group is to use each subject as his own control. Change in the subject may then be measured using as a baseline the premorbid level of adaptation of the patient, or the premorbid level of whatever variable is being measured. Or, one could attempt to assess the level along the variable being measured at the time the patient enters Agency X, when he leaves the agency, and again at some specified time when seen in a followup interview. I have used this type of internal control in a recent study of a pathway agency (Landy and Greenblatt. n.d.).

But researcher and agency should be aware of the fact that this is *not* a substitute for a control group type of study. This approach will give us a measure of change within a patient over time. If one knows the patient very well and enough data have been gathered, and if one can proceed on the premise that if the patient had not been sent to Agency X he would have ended up in a back ward of a state hospital, then one *may* be able to infer that the agency did play a part in helping *these* patients. But, without the control group, we can never know whether the change in these patients would not have happened in the case of a disposition other than being sent to Agency X, for example, simply being discharged into the community without further treatment. Now we may assume that enough clinical experience has now been accumulated that we can say with much certainty that such patients would not have done well in the community—but again, without the control group, we have no scientific

basis for this assumption.

So, self-controls answer some kinds of questions, comparison groups others, and randomly selected control groups still others. Only the use of a control group will enable the researcher to conclude with a relatively large degree of confidence that the effects of the agency made a measurable difference in the rehabilitation outcome of the patient. The other procedures must be buttressed with a wide array of corroborating evidence, but none can lend the conclusions of the researcher as much substance or confidence. (Amplification of these and other points regarding controls will be found in GAP Report 42, 1959.)

Use of Clinical and Service Personnel as Researchers

It is commonplace in rehabilitation research to ask a social scientist to design, direct and execute the study, but to utilize existing personnel in the agency wholly or partially as researchers. Administrators see many advantages accruing from this:

(1) It may be less expensive. (2) It will afford the often underpaid service staff a chance to add to their earnings temporarily by receiving some pay for "doing research." (3) It will make for friendlier relations between service persons and researchers, and lessen feelings of estrangement or threat. (4) It will give service personnel a stake in the research, thereby motivating them to work diligently at it. (5) It will offer service personnel some experience as part of a research team. (6) It will provide the researcher with assistants who are already familiar with the agency. (7) It will make for better rapport with the subjects if they are studied by clinically trained persons.

While all of these reasons may seem valid to the administrator, from the researcher's point of view there are distinct disadvantages in using service personnel as researchers:

(1) Most importantly they are usually untrained in research methods, particularly of the kind which should be utilized in most evaluations of agencies or treatment. (2) It is uneconomical use of the researcher's time to have to train service personnel in basic research methods—it is also unlikely that the administrator will permit sufficient time away from their regular service functions for such training; it is additionally unlikely that service personnel will wish to undergo such training. (3) Even if he should succeed in training such personnel, or find that they already had such training, the researcher still needs to train them in the particular techniques of the project at hand. Again he is unlikely to find that administration will allow sufficient time for this. If given the full-time services of service personnel to do research, he is unlikely to find that the latter will wish to submit to such intensive, rigorous training for a type of skill in which temperamentally they are uninterested. (4) If service personnel are utilized as researchers on a part-time basis, while still functioning within the agency, they still have a professional and emotional stake in the outcome of the research as rehabilitators; therefore the very quality which appears to be an advantage from the viewpoint of the administrator is a disadvantage to the researcher in that it will hinder objective judgments and tend to bias results. (5) Generally speaking, it hardly seems probable that service personnel will feel friendlier toward the researcher if they must also take orders from him as research director; in fact, antagonism toward him may burgeon when they view him as a "boss." Unless service personnel are given time, and they themselves are willing to submit to the kind of training mentioned above, their usefulness as researchers is limited. Furthermore, they may be deceived into believing that they are effectively functioning as researchers when they are not; therefore the research "experience" may be a very deceptive one. (7) To the extent that service personnel still maintain service functions while performing as researchers, they must serve two masters at once; this may stimulate a good deal of role conflict, and in fact reduce their effectiveness as practitioners as much as their competence as researchers. (On these as well as other points made herein, the reader is referred for clear, detailed explanation to Selltiz, Jahoda, Deutsch and Cook, 1959.)

Discussion

I have attempted to review some of the problems that arise in the design and execution of research in agencies engaged in psychiatric rehabilitation. The discussion has centered around defining the problem to be researched; clarifying premises and goals that motivate the work of the agency; establishing meaningful, measurable criteria for the evaluation of rehabilitation status or outcome or level; using controls of some type in order to establish scientific validity and reliability; and problems that may arise from the use of clinical and service personnel as members of the research team.

These are only some of a wide complex of problems that face the researcher in rehabilitation in psychiatry. Several years ago the Community

Services Committee of the National Advisory Mental Health Council set up a subcommittee to study the work that had been done in evaluation of mental health activities. The research literature was exhaustively examined and a report and review published in 1955 (N.I.M.H., 1955). The committee found the following.

> . . . The Committee was impressed with certain findings which seemed to indicate the need for more adequate research in this area. The review uncovered a seeming duplication of effort of investigators in repeating studies of comparable nature, consistent omission of evaluation attempts in specific areas where the need for assessment is great, and repetition of apparent errors in design and methodology committed by previous investigators. . . . It should be recognized . . . that repetition of research studies by a variety of investigators has some inherent value for the purpose of validation, for the purposes of discovery of new knowledge that might accrue from the inclusion of additional variables contributed by differences in settings . . . and for the value that results in repeating a study in order to elicit involvement and participation of numbers of individuals in the problem of mental health.
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> . . . Another finding was the relative paucity of evaluation studies at the exploratory level, in which new leads to the solution of mental health problems must be awaiting discovery. The emphasis thus far has seemed to indicate that effort has gone into following preconceived empirical concepts and treating the results as if they were hypotheses already well-tested and requiring only additional validation. . . . On the whole, most of the studies in the literature and in progress are of cross-sectional design, which seem to defy the tenets of methodology that must be applied if evaluation in mental health is to be valid.
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> . . . An obvious finding is the thinness of the efforts at evaluation. They appear to be diffusely dispersed over the entire field of mental health activities, with little concentration of effort and with weak attempts at combined attack upon any single area. As great as anything else is the need for an approach to evaluation in a form which is highly focused and concentrated. A "dribble" of effort here and there can only promise little in the way of meaningful results that will widen horizons of knowledge.
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> . . . Still another consistent finding is a confusion of levels of conceptualization. The admixture of levels of hypothesis, theory, goal, activity, and result, as well as of concepts on etiology, prevention, prognosis, diagnosis, treatment, individual, group, discipline ideologies, and community influence has eventuated in lack in clarity of the value of accomplishment. Concurrent with this has been unvalidated subscription to value judgments, and an emphasis on evaluation in areas of high interest to particular investigators and communities, irrespective of needs which may have really higher priority for evaluation in terms of ultimate meaningful result. (N.I.M.H., 1955, pp. 56-58.)

It is apparent that the process is not a simple one, but neither is it an impossible one. It would be ridiculous to propose that research *must* be done in order for progress to be made in the field. The history of medicine and of social change generally demonstrates that fields of knowledge and application evolve by empirical trial-and-error as well as through careful research. But such progress, if indeed it can be called that, will be a constant series of "startings from scratch," of beginning anew each effort with little assurance that the energy to be expended really will be compensated by results.

I shall go so far as to say that no research at all may be preferable to investigative labors that go under the name of research which do not attempt in some way to meet the kinds of prerequisites discussed here, and the others that are the hallmarks and canons of scientific endeavor. The task calls for hardheadedness and steadfastness on the part of administrators, clinicians, and researchers alike.

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Dynamic Occupational Therapy

H. AZIMA, M.D.

In the last few years it has become evident that occupational therapy as it is presently practised shows a considerable deficit as far as a background systematic theory is concerned. A previous partial survey[1] indicated that no attempt had been made to put the activities and the events of occupational therapy into a comprehensive conceptual framework.

Due to this lack and the growing need to systematically consider O.T. setups, an outline of a theory of occupational therapy based upon psychoanalytic premises was proposed in 1958.[2] This was the conclusion from several previous studies which involved much of the O.T. media.[3-6]

The purpose of this paper is to examine in detail the theoretical formulations previously outlined. By necessity, there is some repetition but we will attempt to confine discussion to the additional information gained during the past two years. The subject will be developed under two headings: traditional function of O.T. and the proposed function of O.T. The emphasis will be placed upon "function" due to the fact that clarification of this aspect of the problem will lead to a natural understanding of the meaning of O.T.

I. Traditional Function of Occupational Therapy

As the name implies, O.T. was thought of as the use of "occupation" in rehabilitation of mentally ill. Implicitly or explicitly throughout the years the activities of O.T. personnel were extended to include many spheres of therapeutic utility, and led to what seems to be a premature division of this field into pseudo-specialties such as recreational therapy, music therapy, rehabilitation, activity therapy, etc. Condensed as a whole, three sets of functions can be extracted as common denominators of all these varied activities: occupation, education and expression. Occupation and education have been the traditional functions, while expression has been introduced as a more sophisticated explanatory concept for previously known sets of activities. As far as can be determined, no systematic endeavor has been made to render comprehensible the functions of occupation and education used in O.T. in a psychodynamic frame of reference.

From McGill University, Department of Psychiatry and Allan Memorial Institute, Montreal, Canada.

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Hendrick's introduction of "work principle"[7] as a third additional principle in psychoanalysis (the two others being pleasure and reality principles), metapsychologically speaking, has not been received enthusiastically. Moreover, Denber's recent studies on work therapy are more sociological than dynamic[8] and his observations have been mainly preoccupied with integrating work into other therapies used in his wards.

The function of "expression" is a by-product of the concept of abreaction of early psychoanalytic models and has been used often as an explanatory idea without due consideration to metapsychology. It was this paucity of coherent theoretical framework which led us to the proposal of a tentative theoretical scheme based upon psychoanalytic principles which will be outlined presently.

II. The Proposed Functions of Occupational Therapy

The main reason for emphasizing functions of O.T. is that a natural line of inquiry may be developed leading to the delineation of O.T. and an understanding of its meaning. Functions of O.T. can be envisaged under three headings: diagnostic, change detection, and therapeutic.

(1) *Diagnostic Function of O.T.* The media used in O.T. are aptly suited for diagnostic purposes because of the projective component of free creativity inherent in any object-making. We have designated as "projective material" all the O.T. media, contrasting it with "projective test" used in clinical psychology. As in projective tests, the patient projects his internal world into the projective material. There are advantages and disadvantages of projective material vs. projective tests.[9] The main disadvantage is the lack of constancy and a series of "norms" from which inferences can be made about psychopathology. The main advantage is this very lack of constancy which prevents learning and the variation in media which allows the projection of different aspects of personality.

To systematize this diagnostic function, we have proposed a diagnostic scheme which consists of the following:

a. *Diagnostic Battery.* This includes three media: pencil and paper; finger painting, clay or plasticine. The patient is given these media serially, one after the other, and is asked to "draw what comes to his mind," "to paint what comes to his mind" and "to make what comes to

his mind." The reason for the selection of these particular media was the observation that they represented decreasing degree of control. Putting it another way, they could be perceived as a suitable screen, with an increasing degree of projection of primary process modes of object-relations.[10]

b. *Diagnostic Procedure.* This is divided into four phases: (1) preparation phase, i.e., the phase during which the patient approaches the objects and is used for the purpose of behavioral observations; (2) production and completion phase, i.e. the phase of actual involvement with the battery; (3) association phase, i.e., the phase during which the patient is asked to "say what comes to his mind" about his creations; (4) interpretation phase, i.e., the phase of diagnostic interpretations based upon the verbal, non-verbal and the battery of test information obtained from the patient.

c. *Diagnostic Scale.* A tentative diagnostic rating scale has been evolved using the method of "dynamic cluster approach," which we have previously applied to Rorschach.[16] This indicates that the scale is divided into clusters according to the structural premises of the mental functioning, in addition to the parameter of mood. These sectors are: organization of ego, of drives, of object relations, and of mood. Each cluster is composed of different items which are thought to represent a given parameter of psychic structure. Schematically considered, the scale would be something like the following:

Diagnostic Rating Scale

DIAGNOSTIC INDICES

D—Drawing
F—Finger Paint
C—Clay
P—Plasticene

A. ORGANIZATION OF MOOD (elation-depression, anxiety) *Elation-Depression*

1. *Use and Handling of Color (F. C and P)*
   a) Degree of control—from "very controlled" to "no control."
   b) Intensity of color—from "very intense" to "no intensity."
   c) Extensity of color—from "very large" to "small."
   d) Range and purity of color—from "mixed" to "no color."
   e) Texture of color—from "very thick" to "none."
2. *The Use and Handling of Form (D, F, P, C)*
   a) Control of form—from "controlled" to "symbolic."
   b) Form-movement—from "very mobile" to "immobile."
   c) Extensity of form—from "whole" to "part."
   d) Purity of form—from "mixed" to "impure."
3. *Speed of Response*—from "very fast" to "slow."
4. *Tone of Content*—from "very happy" to "very sad."
   —from "animate" to "inanimate."
   —from "human" to "non-human."
   —from "symbolic" to "comprehensible."
5. *Number of Responses* (objects made in each media)—from "many" to "unique."

ANXIETY

1. *Use and Handling of Color*
   Color shock—from "marked" to "none."
   Clarity—from "very clear" to "chaotic."
2. *Use and Handling of Form*
   Distinct—shading—indistinct.
   Continuity—discontinuity.
   Controlled—uncontrolled.
   Smooth—shaky.
3. *Movement*
   Blocking—rapid movement.
   Smooth flow—choppy.
4. *Tone of Content*
   Overt anxiety.
   Covert anxiety.
5. *Texture*
   Degree of shading.
   Degree of smoothness.
   Degree of fuzziness.

B. ORGANIZATION OF DRIVES

1. *The Nature of Drives*
   a) Libidinal drives
      1. Content: overt libidinal content; covert libidinal content (symbolic).
      2. Degree of form control.
      3. Degree of intensity of color, texture, movement.
      4. Mode of object handling (stroking, rubbing, messing, soiling, smearing, licking, to and fro).
      5. The behavior towards the therapist and objects.
   b) Aggressive drives
      1. Content: overt aggressive content, covert aggressive content.
      2. Degree of form control.
      3. Degree of intensity of movement (energy output).
      4. Mode of object handling (scratching, nailing, twisting, pressing, cutting, breaking, smashing, etc.)
      5. Behavior towards therapist and objects.
2. *Content of Drives*
   a) Oral (libidinal-aggressive)
      —active to passive responses.
      —overt to covert and symbolic responses.

b) Anal (libidinal-aggressive)
—active to passive responses.
—overt to covert and symbolic responses.

c) Phallic (libidinal-aggressive)
—active to passive responses.
—overt to covert and symbolic responses.

C. ORGANIZATION OF EGO

a) Synthetic functions

1. Degree of organization of form, color, movement.
2. Degree of organization from one medium to another.
3. Use of the battery.
4. Total approach to the battery.
5. Completeness—incompleteness.
6. Comprehensibility—incomprehensibility (the degree of preponderance of secondary and primary processes).

b) Defensive functions (inferred from creations and associations)

Repression
Reaction formation
Isolation
Undoing
Projection
Splitting
Introjection
Withdrawal
Denial
Regression

D. ORGANIZATION OF OBJECT RELATIONS

1. Relation to the therapist
—libidinal-aggressive
—indifferent
—inhibited
—problematic
—realistic
2. Relation to the object
—libidinal-aggressive
—indifferent
—inhibited
—problematic
—realistic
3. Content of the object
—human (mobile-immobile)
—animal (mobile-immobile)
—vegetal
—inanimate
—void
—bizarre
4. Structure of the object
—recognizability
—culture-sytonicity
—relation of parts
—completeness-incompleteness
—realistic-symbolic

(2) *Change Detection Function.* The projective material of the diagnostic battery, due to its lack of constancy, and due to the fact that it allows "free projection" (in contrast to "directed projection" of projective tests) of phantasy object-relations is not subject to learning and hence can be used repeatedly at short intervals. This characteristic makes it a useful tool in evaluation of change in psychic process, not only as a diagnostic aid, but also as an instrument of research. Experience has revealed[10] that projective material has both stability and flexibility as a change evaluator.

Up to the present we have used this function of O.T. in the following areas: a) Detection of regression-progression sequence in different therapeutic procedures; b) Detection of mood changes in pharmacotherapy of manic-depressive states where a combination of tranquilizers and antidepressants are required; c) Detection of changes in body-image and the degree of disorganization in studies with psychomimetic substances.

(3) *Therapeutic Function.* Manifold functional possibilities of O.T. can be understood through three concepts of exploration, gratification and integration, where the parameters of psychic structures are emphasized differentially.

A. *Exploration.* By that is meant that O.T. media are utilized in the uncovering of and working through of unconscious processes. We have put all such attempts under the title of "projective therapy," group or individual.[6,9] We have abandoned the term "analytic art therapy" to designate such a technique because of its implied aesthetic connotation, and also because in the "projective therapy" the problem of free creativity was systematized and it was necessary to delineate it from the general use of "art" in psychotherapy.

The term "projective" indicates one of the main dynamic characteristics of the technique, i.e., the projection of the internal world into the external objects made available to the patient. Briefly described, the therapeutic procedure consists of the following: (1) Objects consisting of pencil, color crayons, paper and colored plasticine; (2) Free creation period, the non-verbal opening phase of each session lasting from 15-30 minutes; the patient is asked to "make what comes to his mind" with the objects. (3) Free association period. This is the verbal phase, lasting from 1-1½ hours, during which the patient is asked to "say what comes to his mind" about his creations, or those of others in a group situation. Experience has demonstrated that the sys-

tematic use of the free creativity in this manner seems to have a facilitatory effect on the uncovering of unconscious processes related to defenses, drives and object-relations. In addition, a certain degree of non-verbal discharge and recanalization of drives seems to take place due to the tactile and muscular involvement with actual objects which projectively can represent different phantasied object-relations.

B. Gratification. The provision of possibilities for gratification of drives. This is an id directed therapeutic approach which may be realized directly or indirectly.

1—Direct gratification—A decrease in the intensity of pre-genital drives where the basic conflicts originate. The gratification can be attempted through making available to the patients what can be considered as primitive oral and anal media, such as a baby bottle, pacifier, milk, clay, mud pies, coco mud, etc. Experience has revealed that the realization of this gratification can occur only in certain specific therapeutic settings which can be designated in general as "anaclitic situation." The term indicates the development of a situation of total dependency which finally can be symbolically experienced as that of a good-mother-child (anaclitic) relationship. This anaclitic state can be established only after a massive regression to the oral mode of existence has occurred. Gratification of basic needs in such a situation was previously attempted in two sets of experiments: what was called object-relations therapy in very regressed schizophrenics[3,4] and anaclitic therapy produced by drugs,[11] by prolonged sleep and electric shock,[12] or by perceptual isolation.[13] In addition, recently it has become apparent that object-relations therapy, i.e., using of primitive media in an anaclitic situation may be the treatment par excellence of certain acute psychotic episodes.[14]

2—Indirect gratification of needs and the decrease of instinctual tension not directly as in anaclitic relationships but through a decrease in super-ego pressure, and super-ego reinforcement or atonement. The change in super-ego attitudes which was implicit in object-relations therapies is made explicit here. This may be achieved either actively (by work or by suffering) or passively (by receiving praise).

C. Integration. The integration of different psychic functions is implicit in the two previously mentioned functions. In exploration techniques, integration is achieved through uncovering and working through; in gratification techniques through a decrease in id or super-ego pressure, and a reorganization of functional investments. By integration here, we are particularly concerned with the ego-integrative functions, i.e., the consideration of the difficult problem of ego-strengthening which has been claimed —but never systematically studied—by many as one of the major functions of O.T. This has been, and still is, the area where many have tried to pigeon-hole O.T. either on dynamic or non-dynamic basis.

It is very difficult and theoretically questionable if one can alter the ego structure directly and permanently by psychological means available in O.T. Changes in the ego structure may be brought about in the following ways:

1—Indirect change. The ego may be indirectly influenced through a decrease in id tension or super-ego pressure. By allowing the discharged of dammed up libidinal and aggressive tendencies, or the diminution of super-ego pressure through temporary introjection of a good external object (by encouragement and reward), a relative increase in the ego's capacity to master the impulses and integrative powers may occur. At least this is a theoretical possibility.

2—Direct change. As far as influencing the ego directly, one has to consider the elemental components of what is called "ego," and then see if any of them can be influenced directly in the direction of strength with the means available in O.T.

The ego can be conceptualized as a set of functions which can be divided into two well-known categories of autonomous[15] and defensive functions.

Among the autonomous functions, there are three which may be influenced directly, namely, perception, thinking and motor action. One can educate patients to perceive more adequately their environment, to think more logically, and to use their musculature. However, this does not imply that the psychopathological problems are changed. In fact, it seems doubtful if reinforcement of these autonomous functions as such without the uncovering of the conflicts leading to their improper functioning in reality testing would be possible.

Among the defensive functions, one can say as a matter of principle, that psychotic defenses (manic-depressive, schizophrenic) should not be reinforced. As far as the neurotic defenses are concerned, again it is problematic that one can directly influence these unconscious mechanisms. The only thing that can be expected may be the

reinforcement of behaviorally observable aspects of some of these defenses: (a) reaction formation. In decompensating obsessive compulsives, encouragement of activities requiring meticulousness and detailing (sawing, weaving, rug-making, etc.) may help in controlling anxiety and establishing the obsessive defenses. (b) Reinforcement of counter-phobic attitudes, either in the form of guidance about avoiding certain anxiety provoking situations, or by forcing the patient to control the situational anxiety by repetition and gradual mastery. (c) Suppression and forced substitute reinvestment of interest, by diverting the patient's attention from inner to outer happenings.

It should be noted that in all these attempts to reinforce certain defenses, the problem of object-relations is implicit and the occupational therapist probably operates as a good super-ego surrogate.

Summary

An outline of a theory of occupational therapy based upon psychodynamic concepts is presented. It is suggested that the application of these concepts expands the frontiers of O.T., increases its range of applicability, and provides a comprehensible theoretical background.

The functions of O. T. were considered to be threefold: diagnostic, change detection and therapeutic.

Diagnostic function was attributed to the usefulness of the O.T. media, which was called "projective material," contrasting and aligning it to "projective tests," in that O.T. media provided a suitable projection screen for the internal world. A diagnostic schema, including a diagnostic rating scale was presented.

Change detection function was attributed to the relative lack of learning problem in the repetitive use of the projective material.

Therapeutic function was envisaged under the concepts: exploration, gratification and integration. Exploration involved the systematic use of free creation in the uncovering and working through of unconscious processes. Gratification implied direct decrease in id tension or indirect relief of super-ego pressure by the induction of a state of anaclitic relationship and the provision of primitive objects. Integration indicated the problem of direct or indirect influence upon the ego organization by alterations of autonomous and defensive functions.

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Psychopharmacology in Rehabilitation of the Chronic Psychotic

SIDNEY MERLIS, M.D.

It is not often that progress in medical science proceeds so rapidly that one may witness the introduction, development and broad effective application of a significant therapy for a major disease within a period of a few years. Today we are fortunate to have such an experience with regard to the use of pharmacological agents in the management of mental illness. Some of us have been interested observers, most of us here have been active participants. In less than a decade the entire philosophy regarding mental disease and its ramifications have been permanently altered. The psychotropic drugs, in addition to their obvious importance in treatment, have had profound secondary effects on our overall thinking particularly on the social influences which concern us greatly insofar as the management of the psychiatric patient is concerned. These secondary effects are reflected in our present day hospital programs such as the "open door policy" and the "therapeutic community." It has also influenced the more active utilization of out-patient facilities such as "half way houses" and "after care clinics."

These new drugs have produced a more active acceptance of various rehabilitative techniques aimed at returning psychiatric patients to the community and arranging for their productive absorption into the economic and social framework of society. Like most of our experiences in psychiatry, work with the psychotropic agents and the problems of rehabilitation of the mentally ill have gone through two definitive stages. The first stage was a general non-discriminative application of various drugs and techniques resulting often in broad claims of effectiveness. The second phase included the development of analogous procedures and compounds all having relatively similar action and properties but with supposedly specific significant differences. It was these differences which were considered the major reason for their introduction into clinical use. It was at this point that much confusion developed. Paradoxical reports become rampant. Clinical appraisals became more critical. This is the stage of our present development. The third period is by far to be the most important. It is toward this cycle that we are currently moving. Here definitive techniques and discriminative applications are clarified. This is the stage of sober reappraisal.

It is here that fundamental patterns are laid down which serve as major reference points for future programs in treatment. I would like to address myself to a realistic discussion of the role of psychopharmacologic agents and rehabilitative techniques in chronically ill mental patients. Let me preface my remarks by stating that I am not a therapeutic nihilist. However, the proper advancement of science and therapeutic medicine for the benefit of all must be done with a minimum of affective preconceptions and a maximum of objective reality.

Brill and Patton[1] in their analysis of the reduced hospital population observed a significant decrease in mental hospital patients between the years 1955 and 1958. They considered this lowered census related to the introduction and widespread use of tranquilizers in the management of mental disease. They do not exclude the significance of parallel improvement in the liberalization of hospital policies or intensified treatment programs as well as other factors. These statistics as well as other reports in a similar vein have been used as highly effective instruments for obtaining increased appropriations from state and federal government agencies for the expansion of existing facilities and programs and for the development of new ones.

For the most part the newer facilities are merely an extension of the old. New structures are built, additional research activities are established, impressive paper programs of clinical facilities are inaugurated. Yet little attention is paid to the fundamental problem of staffing and personnel. It is simpler, from an administrative point of view, to look with pride to a new building as an example of progress than to deal with the needs of personnel. Buildings require only periodic coats of paint. Personnel are dynamic factors requiring constant attention. Their drives for elevation of their own status as well as their motivation for improved patient treatment and patient facilities are a constant source of irritation for the administrator. Little is said of the inadequate salary scales of hospital em-

From the Research Division, Central Islip State Hospital, Central Islip, N. Y.

ployees. It is obvious that the good care the patients receive from the hospital personnel is a measure of their devotion to their work in spite of financial sacrifice. The research units authorized by administrative decree often are ineffective for want of adequately trained research people. Little is said of the long waiting lists at out-patient clinics due to lack of therapists. You might ask what the foregoing has to do with the subject to be discussed. The answer is this. In rehabilitation particularly with the mentally ill, the secret of success lies not in the physical plants surrounding the individual but in the attitude, training and motivation of all personnel toward effective restoration of the disabled person to an appropriate place in society.

While the use of broad generalizations sprinkled with a liberal helping of statistics serve to produce an image of glowing successes, close scrutiny reveals many difficulties and inadequacies relatively untouched by the newer progress in psychiatric practice. The chronic psychotic is the most glaring example of our inadequacies. The newer drug treatments and rehabilitative techniques have been helpful primarily in our acute and subacute psychiatric disorders and it is in these groups that most of the positive results are recorded. It has been insinuated that because we are increasingly successful in our management of the short-term mentally ill patients, the chronic group will gradually disappear through the simple process of inanition. This I believe is wishful thinking.

Rehabilitation in most simple terms means "a restoration to a former capacity." (Websters New International Dictionary, Second Edition, Unabridged, 1957.) While this is a seemingly simple definition certain inherent limitations must be noted. Goals for psychiatric rehabilitation must be in keeping with the general principles of medicine. Medicine is not a curative science. Treatment is directed primarily to the relief of symptoms and until further knowledge into etiology is established this is the best we can do.

When we speak of the former capacity of a psychiatric patient several problems must be considered. First the pre-morbid personality may have been so impaired that restoration alone is not a practical solution to returning this individual to society. Second, particularly in the case of the chronic patient, restoration requires an almost complete program of re-education. This is often impossible due not only to the inadequacies of our procedures but also to the innate resistance of the patient who because of his illness cannot accept the restrictive demands of the modern community. It has been recognized that as civilization develops there is a corresponding increase in the number of restrictions, taboos and inhibitions demanded of the individual. In our present level of society in the United States these factors significantly mitigate against an easy assimilation of the mentally ill.

The hospitalized patient has been ejected from society because of symptoms disturbing to his relatives or neighbors. This ejection, most often involuntary, implies that the individual must not return to the community until he can learn to behave in a way acceptable to his fellow man. Thus, it is the duty of the psychiatric hospital by means of its various treatment programs to condition the patient so that his future behavior will be appropriate and acceptable.

Psychiatric rehabilitation as it now functions proceeds on four distinctive levels:

First is a return of the patient to the community to function as an individual self-supporting normal member of society. He requires no help, no special programs, no psychiatric support. These are patients who are usually mildly ill, suffering from relatively minor brief periods of emotional decompensation and who represent our best advertisement in terms of effective psychiatric treatment. These people, because of emotional instability reactions, behave in an impulsive manner resulting in a period of hospitalization. Usually they appear quite stable and normal shortly after hospital admission and are often quickly discharged with or without mild forms of drug therapy.

The second level concerns the patient with a more serious illness whose condition is such that his return to the community requires various degrees of medical, social and economic support. The success of such a program depends not only on the patient but upon the charitable responsiveness of his environment. He represents a significant burden to his community. The amount of such a burden that society is willing to tolerate varies in considerable degree.. This patient with an affective and/or integrative disorder is frequently unpredictable in his behavior. Drug therapy is used with fair effectiveness in controlling the symptomatology although many of these patients are inconsistent in taking their medication. This may significantly alter their level of psychiatric compensation. Many have been only partially conditioned by their periods of hospitalization. They have learned much dur-

ing their illnses, particularly in regard to contact with the physicians and ward personnel. In a relatively stable environment their limited capacity for adjustment is not strained. They quickly perceive what is required of them for hospital discharge. Most have not been hospitalized long enough for them to lose their motivation to return to society. It is these people who may say in strict confidence "of course I still hear voices and I know that they are after me, but I will not tell this to the doctor for he'll not let me out if I do." These people do leave the hospital and become embroiled in a highly competitive way of living. Their limited tolerance and their low frustration threshold requires an active manipulation of all the supportive forces, medical, social and economic, to permit them to retain a tenuous grip on their environment. Many of these people perform inadequately in job situations. They often work at levels well below their capacities. Many maintain an unstable psychological status with cyclic patterns and exaggerated responses to relatively minimal stresses. These people frequently get into difficulty often leading to their return to the hospital. This serves to tarnish the good image that psychiatry attempts to establish for itself because to most this represents a failure in treatment.

The third level is a rather recent development. The problem of rehabilitation here meets a major challenge. This group consists of rather seriously ill patients with extensive psychiatric symptoms of an overt nature. This group has been permitted to leave the hospital because of an atmosphere of greater optimism about the outlook of psychoses and an attitude of greater liberalization in the discharge of patients. Many of these people are clinically no better than they were years ago when they were not permitted to leave the hospital, but our current vogue is to discharge patients frequently on a calculated risk basis. It is this group which has contributed greatly to the actual lowering of the hospital census. By actually pushing these people from the hospital we have succeeded in giving the impression that great changes are taking place.

In many ways physicians have become victims of the extensive claims made for the psychotropic agents. Certainly it was because of the effects of these drugs that liberalization of attitudes towards our patients took place. Certainly increased social pressures and enthusiastic claims for the effects of the newer treatment methods in psychiatry are responsible for what appears to be premature hospital discharge. Due to extensive coverage of medical subjects in the lay literature the public has been encouraged to expect increasingly spectacular results. Informal competitive practices arise from the regularly published lists of statistics concerning the movement and treatment activities of different hospitals. There is a certain ego satisfaction derived from the knowledge that your hospital surpasses another in low percentage of restraints in use, the limited use of seclusion room and the relatively high incidence of "open door patients" and discharge rates. It is a great satisfaction to many to see statistics demonstrating a high percentage of "cures," "complete remissions" and other phrases indicating satisfactory treatment responses. Very few hospital workers ever have the opportunity to observe this group of patients after they are discharged. We leave it to the social agencies and the visiting nurses to follow these people as they attempt to adjust to the demands of society. In many cases the misery, the inconvenience, the unhappiness and the hostility which has encompassed the families who are caring for these seriously sick patients often wipes out any of the good that has been accomplished through broadened understanding of the mental disease problem. In spite of the various tranquilizing drugs with which he is supplied, this chronic psychotic patient in the home frequently becomes the center of all interest and controversy. He is often antagonistic, hostile, rigid and demanding. He is usually indolent and unpredictable in his behavior. There is generally lethargy and withdrawn behavior.

All but the most guilt ridden families must feel that somewhere along the line a gross error in clinical judgment has been made. Yet the statistics announce the lowering of the hospital census. This is not rehabilitation.

The fourth level of rehabilitation involves the hospitalized patient who remains in the hospital. Strangely enough it is here, I feel, that we have made our greatest progress.

In the modern psychiatric hospital we have created a situation in which the patient can easily adapt. That this in itself can be a goal in treatment is most difficult for many people to accept. To many it implies a degree of failure but actually this is not truly the case. We are teaching these people to lead a life which is far more productive and happy in an environment which is understanding.

In our hospitals it is not criminal to suffer from sexual deviation or narcotic addiction. We accept the alcoholic as a sick person. A mentally

ill patient is not the object of derision and ostracism. In fact our social culture as it exists in our hospitals is more democratic and broader in its views The social pressures and prejudices so prominent in our society are for the most part limited or entirely absent in our hospital population. Many of our long term hospitalized patients have achieved a degree of rehabilitation which otherwise could never have been accomplished. These people who remain in the hospital for months and years, work at regular and useful jobs, partake of recreational activities with friends and enjoy a sense of belonging to a community which offers a greater sense of security and satisfaction than in any other situation available.

The place of chemotherapy in the role of rehabilitation is most significant. We are beginning now, however, to realize its limitations. Regardless of what has been written in the past, the applications of the psychopharmacological agents, as they exist now, are for the purpose of symptomatic effect alone. They do not cure. They are to the sick personality as insulin is to the diabetic. They serve to subdue unwanted psychological symptoms, often producing undesirable physical side effects in the process. There is no such thing at the present time as drug specificity for precise clinical syndromes in psychiatry. We have sedatives, tranquilizers, stimulants and psychic-energizers; they do exactly what their titles imply. These drugs serve to hide or control symptoms so that when successful they permit the patient to be acceptable to society although he is still sick. We can stimulate the depressed patient, we can tranquilize the hyperactive patient and that is in essence the extent of therapy with drugs.

The use of these agents for continuous supportive therapy after discharge from the hospital represents a significant therapeutic advance. Patient relapse rates have been significantly decreased with this regime. Intelligent application of psychotropic drugs can produce a reduction of psychological symptoms so that these patients can receive rehabilitative support under the most optimum conditions that circumstances of the illness permit.

We clinicians have been bombarded with hundreds of medical preparations each claiming significant advantage for the treatment of the sick personality. How do we choose one from another? The answer is strictly by empirical selection and the use of clinical judgment backed by experience, common sense and luck. We can no more standardize a method of drug therapy for psychiatric syndromes than we can standardize the use of digitalis therapy for the failing heart. After we have given the drugs and have produced a response, good or bad, we still have the basic clinical syndrome. The chronic psychotic with milder symptoms may at times be discharged from the hospital under sheltered conditions. The facilities that may be needed must be tailored to fit each patient. Realistic disposition of the chronic psychotic outside the hospital requires a close reappraisal of family attitudes. Bullard et al.[3] in an interesting study have clearly outlined some of the planning problems in this regard.

The severely ill chronic psychotic patient with problems of apathy, seclusiveness, rigidity, dishevelment, confusion, etc., is not a subject for rehabilitation outside the mental hospital. There is a lack of understanding of this basic problem which extends even to the committees of Congress. Reports from both Senate and House groups in 1955 advocated the end of "mental pest houses where patients are confined indefinitely with slight hope of cure."[4] The American Medical Association's Council on Mental Health has indicated a questioning view regarding the mental hospital concept as a primary tool in treatment of psychiatric disorders. Certainly these attitudes reflect the judgment of wise men. Yet one feels that their high principles and their desires for the improved welfare of mentally ill is not entirely in keeping with our present knowledge regarding the realistic care and management of the chronic patient.

In closing I would like to state that the past decade has emphasized symptomatic improvement and hospital discharge. However, until we can do better we must be content to accept for our chronically ill population symptomatic relief and continued hospital existence. Regardless of social, economic or administrative pressures most of these patients must be kept in the hospital. It is only there that adequate facilities for the proper care and management of these people exist.

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Award Presentation

FRANZ J. KALLMANN, M.D.,
Chairman of Awards Committee

It is a matter of great satisfaction to all of us concerned with the administration of the R. Thornton Wilson Award in Genetic Psychiatry, that the brief ceremony of announcing the winner or winners of this prize at the end of our annual meeting has taken on the quality of an honorable tradition. We are particularly proud of this accomplishment, inasmuch as for the first time this year the Awards Committee, currently consisting of Dr. Holt, Dr. Pacella and myself, has been able to operate under well-defined official ground rules.

According to the new set of regulations, two equal prizes rather than one are awarded to contributors of scientific reports within the broad area of genetics, as related to etiologic or preventive problems of psychiatry. One award goes to a research worker in the basic sciences, the other to a worker at the clinical level. Last year I explained that as a *psychiatric* research association we urgently need both groups for our programs—the clinical and the experimental. Only by giving equal recognition can we have meetings that fully reflect all the scientific advances in our discipline.

It may also be noted that preference had to be given to original research reports submitted by a certain date, long before the actual meeting.

We have made every conceivable effort to apply these provisions fairly and we hope they will help make friends for our Society.

An immediate effect of these regulations was to reduce the number of eligible participants in each section, at the same time raising the qualitative level to such a point that the application of even the most refined rating system has virtually become a lottery. The differences between the ratings are so infinitesimal that the awards could have gone to everyone. The outcome of this contest was even closer than that of the 1960 presidential election.

With these stipulations in mind I take much pleasure in announcing that the R. Thornton Wilson Award in the basic sciences goes to Dr. Aaron Bendich of the Sloan-Kettering Institute for Cancer Research. Not only has he performed experimental miracles in one of the least explored areas of human genetics, but he also has a special gift for communicating his findings to clinicians and psychiatrists at large. Dr. Bendich, may I congratulate you on your pioneering work and present to you your well-deserved prize.

The R. Thornton Wilson Award for clinical research goes to an equally distinguished worker, Dr. Sidney C. Werner of the Department of Medicine of Columbia University. His achievements in unraveling the complexities of thyroid disorders are so well known that they need not be enumerated here. He is the editor of a standard text in this field which has been so successful that it will soon appear in a second edition. Dr. Werner, my heartiest congratulations.

May I say how much I regret that we don't have five or six more prizes to confer. There isn't a single participant in this excellent symposium who would not have deserved a prize, too. My thanks to all the speakers who contributed so generously to the success of this stimulating symposium.

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Ossining, N. Y.

Brody, Matthew
41 Eastern Parkway
Brooklyn 38, N. Y.

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Kings Park State Hosp.
Kings Park, N. Y.

Cammer Leonard
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824 S. Arlington Mill Dr.
Arlington, Virginia

Cancenllieri, Reno
1395 Pelham Parkway N.
New York 67, N. Y.

Cares, Ruben
Kings Park State Hosp.
Kings Park, N. Y.

Carey, Alice T.
110 Echo Avenue
New Rochelle, N. Y.

Carey, Justin P.
110 Echo Avenue
New Rochelle, N. Y.

Carey, Thomas C.
111 Gillett Street
Hartford, Conn.

Carlozzi, Michael
630 Flushing Avenue
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86 Voorhis Avenue
Rockville Centre, N. Y.

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43 Narcissus Drive
Syosset, L. I., N. Y.

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Belle Meade, N. J.

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Brooklyn, N. Y.

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250 East 200th Street
New York 58, N. Y.

Cassino, Frank A.
119-36 80th Road
Kew Gardens, N. Y.

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Rome, Italy

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New York 21, N. Y.

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1750 Grand Concourse
New York 57, N. Y.

Dhrymiotis, Andrews D.
8924 164th Street
Jamaica 32, N. Y.

Diamond, Oscar K.
80-45 Winchester Blvd.
Queens Village 27, N. Y.

di Cori, F. A.
40 Fifth Avenue
New York 11, N. Y.

D'Isernia, Richard
16 North Broadway
White Plains, N. Y.

Dixon, Robert E.
11 West 74th Street
New York, N. Y.

Dodds, Harold H.
604 Plant Street
Utica, N. Y.

Doltolo, Joseph
115 E. 61st Street
New York 21, N. Y.

Dorfman, Wilfred
1921 Newkirk Avenue
Brooklyn 26, N. Y.

Dumas, Kenneth J.
c/o Pfizer Labs.
630 Flushing Avenue
Brooklyn 6, N. Y.

Dunlop, Edwin
9 School Street
Attleboro, Mass.

Eisenberg, Morton S.
68 East 86th Street
New York, N. Y.

Eliasberg, W. G.
151 Central Park West
New York 23, N. Y.

Elpern, Sidney
1749 Grand Concourse
New York 53, N. Y.

Epstein, Joseph
975 Park Avenue
New York 28, N. Y.

Eyres, Alfred E.
17800 E. 8 Mile Rd.
Detroit 36, Mich.

Falek, Arthur
65-49 164th Street
Flushing, N. Y.

Falsey, Edward F.
237 77th Street
Brooklyn 9, N. Y.

Fenichel, Maurice
Kings Park St. Hosp.
Kings Park, N. Y.

Folmer, Edward J.
15 East 36th Street
New York, N. Y.

Fosco, William N.
1669 Astor Avenue
New York 69, N. Y.

Foxe, Arthur N.
9 East 67th Street
New York 21, N. Y.

Freed, Herbert
Medical Tower Building
255 South 17th Street
Philadelphia 3, Pa.

Friedland, Alvin
49 So. Munn Street
East Orange, N. J.

Friedman, Emerick
497 State Street
Albany, N. Y.

Friedman, Jacob H.
1749 Grand Concourse
New York 53, N. Y.

Furst, William
50 So. Munn Avenue
East Orange, N. J.

Gabriel, Anthony R.
108 East 81st Street
New York 28, N. Y.

Gagliardi, Francis
177-30 Wexford Terrace
Jamaica, N. Y.

Gahagan, Lawrence H.
133 S. Lasky Drive
Beverly Hills, Calif.

Gallinek, Alfred
1165 Fifth Avenue
New York 29, N. Y.

Gibson, Augustus
Merck & Co.
Rahway, N. J.

Gilbert, Michael M.
316 N.E. 14th Terrace
Miami 32, Florida

Goldfarb, Charles
43 King Street
New York 14, N. Y.

Goldman, Douglas
179 E. McMillan Street
Cincinnati 19, Ohio

Goldman, Max
176 Bay State Road
Boston 15, Mass.

Goldstein, Louis
599 West 190th Street
New York 40, N. Y.

Gordon, Hirsch L.
239 Central Park W.
New York 24, N. Y.

Gralnick, Alexander
High Point Hospital
Port Chester, N. Y.

Greenhall, Armand L.
123 West 86th Street
New York 24, N. Y.

Gruenthal, Max
25 West 81st Street
New York 24, N. Y.

Hand, Morton
1620 Ditmas Avenue
Brooklyn 26, N. Y.

Handin, Irving L.
129 Country Club Drive
Elmira, N. Y.

Hankoff, Leon D.
387 Parkside Avenue
Brooklyn 26, N. Y.

Harty, John E.
101 N. Main Street
Waterbury 54, Conn.

Heller, Saul I.
11 East 68th Street
New York 21, N. Y.

Hochstetter, Werner
180 Ft. Washington Ave.
New York 32, N. Y.

Hoffman, Carl J.
2901 Cottman Avenue
Philadelphia 49, Pa.

Holt, William L., Jr.
Albany Hospital
Albany, N. Y.

Houck, Knut H.
579 Cottonwood Street
Acaville, Calif.

Hubbard, R. C.
109 Deer Hill Avenue
Danbury, Conn.

Hymowitz, Abraham
52 Sterling Street
Brooklyn 25, N. Y.

Impastato, Arthur S.
Kings Park State Hosp.
Kings Park, N. Y.

Impastato, David J.
40 Fifth Avenue
New York 11, N. Y.

Ivey, Evelyn P.
24 Elm Street
Morristown, N. J.

Jarvik, L. F.
105 Joyce Road
Eastchester, N. Y.

Jones, Charles H.
333 Grotto Avenue
Providence, R. I.

Kalinowsky, Lothar B.
115 East 82nd Street
New York 28, N. Y.

Kallmann, Franz J.
924 West End Avenue
New York 25, N. Y.

Karlan, S. C.
39-15 Main Street
Flushing, N. Y.

Kaye, Jesse J.
395 Quail Street
Albany 8, N. Y.

Kelly, F. W.
1351 Mt. Hope Avenue
Rochester 20, N. Y.

Kelly, John L.
119 North Olive Street
Media, Penn.

Kippen, Arnold A.
1121 Cleveland Ave. NW
Canton 3, Ohio

Korenyi, Charles D.
88-25 148th Street
Jamaica 35, N. Y.

LaBurt, Harry A.
Creedmoor State Hosp.
Queens Village, N. Y.

Lando, Santino
1217 Union Street
Schenectady 8, N. Y.

Lang, H. Beckett
644 A. Madison Avenue
Albany 8, N. Y.

Lapovasky, Arthur J.
887 Ocean Avenue
Brooklyn 26, N. Y.

Lederman, Solomon J.
157 East 18th Street
New York 3, N. Y.

Lesse, Stanley
15 W. 81st Street
New York 24, N. Y.

Leuzzi, Anthony P.
30 So. Broadway
Yonkers 2, N. Y.

Levine, Alexander
790 East 18th Street
Brooklyn 30, N. Y.

Lippman, Abbott
929 Albemarle Road
Brooklyn 18, N. Y.

Lipton, Harry R.
490 Peachtree Street N.E.
Atlanta 8, Ga.

Lipton, Louis M.
1200 Fifth Avenue
New York 21, N. Y.

Locascio, Nicholas
133 East 58th Street
New York 22, N. Y.

Loscalzo, Anthony E.
124 East 40th Street
New York, N. Y.

Lotesta, Pasquale
147 85th Street
Brooklyn 30, N. Y.

Luwisch, Joachim
257 Lexington Avenue
New York 16, N. Y.

Machol, Gustav
228 17th Street
Brooklyn, N. Y.

Malamud, William
The National Assoc. for
Mental Health, Inc.
10 Columbus Circle
New York 19, N. Y.

Marks, Ben
18985 Wildermere Avenue
Detroit, Michigan

Mascort, Juan A.
306 Professional Bldg.
Santuree, P.R.

McCartney, James L.
223 Stewart Avenue
Garden City, N. Y.

McLaughlin, Blaine E.
108 E. Gowen Avenue
Philadelphia 19, Penna.

Mearin, Robert J.
331 Claremond Avenue
Montclair, N. J.

Meisel, Arthur M.
135 Eastern Parkway
Brooklyn 17, N. Y.

Merrill, George G.
100 E. Chase Street
Baltimore 2, Md.

Merwarth, Harold R.
30 Eighth Avenue
Brooklyn 17, N. Y.

Miller, Jacob J.
1749 Grand Concourse
New York 53, N. Y.

Murphy, John M.
147 Melbury Road
Babylon, L.I., N.Y.

Negrin, Juan, Jr.
108 East 81st Street
New York 28, N. Y.

Ogden, Lindsley
406 Massachusetts Ave.
Boston, Mass.

Osinski, Walter A.
25 Upper Loudon Road
Loudonville, N. Y.

Pacella, Bernard L.
115 East 61st Street
New York 21, N. Y.

Padula, Louis J.
2790 Arlington Avenue
New York 63, N. Y.

Page, James A.
522 Midland Avenue
Berwyn, Pa.

Palmer, Lauchlen S.
534 Greenway Road
Elmira, N. Y.

Patry, Frederick L.
1917 14th Street W
Bradenton, Fla.

Pearse, John J.
350 Richmonl Terrace
Staten Island, N. Y.

Pelzman, Oscar
107 No. Ocean Avenue
Patchogue, N. Y.

Perlowitz, Harry
100 East 96th Street
Brooklyn 12, N. Y.

Pinney, Edward L.
1 Hanson Place
Brooklyn, N. Y.

Pritcher, Leon
88820 Wilshire Boulevard
Beverly Hills, Calif.

Pujals, Ramirez Carlos
J. A. Saco 609
Santiago, Cuba

Rainer, John D.
1300 Midland Avenue
Yonkers, N. Y.

Rappa, James
681 Clarkson Avenue
Brooklyn 3, N. Y.

Reback, Samuel
160 Central Avenue
Staten Island, N. Y.

Reiss, Max
Willowbrook State School
Staten Island 14, N. Y.

Remler, Anna M.
2085 Ocean Parkway
Brooklyn, N. Y.

Reiter, Reuben
187 Sylvan Avenue
Leonia, N. J.

Revitch, Eugene
828 Madison Avenue
Plainfield, N. J.

Reznikoff, Leon
42 Robinson Terrace
Clifton, N. J.

Riemer, Morris D.
755 Ocean Avenue
Brooklyn, N. Y.

Robie, Thedore R.
676 Park Avenue
East Orange, N. J.

Rosenbaum, Salo
50 East 72nd Street
New York 21, N. Y.

Ross, Ira S.
179 Irvington Avenue
So. Orange, N. J.

Rozett, Oscar
19 Prospect Street
Summit, N. J.

Rudoy, Martin U.
139-02 Grand Central Pwy.
Kew Gardens, N. Y.

Rupp, Charles
133 So. 36th Street
Philadelphia 4, Pa.

Ryan, V. Gerard
Elmcrest Manor
Portland, Conn.

Ryberg, Percy E.
30 Fifth Avenue
New York 11, N. Y.

Sainz, Anthony
Marcy State Hospital
Marcy, N. Y.

Sarlin, M. Bruce
1040 Park Avenue
New York 28, N. Y.

Schindelheim, Samuel
463 East 19th Street
Brooklyn 26, N. Y.

Shainess, Natalie
19 East 88th Street
New York 28, N. Y.

Shattan, Samuel P.
8247 Lincoln Road
Verona, Pa.

Shultz, Gertrude M.
Lakemont, Yates Co.
New York

Simecek, Victor H.
P.O. Box 148
Fort Ogden, Fla.

Spiegel, Herbert T.
161 Kings Point Road
Great Neck, N. Y.

Squilla, Vincent D.
918 Pelham Pkwy So.
New York, N. Y.

Stein, Calvert
71 Meadowbrook Road
Longmeadow 6, Mass.

Stern, Morton M.
24 Girard Place
Newark 8, N. J.

Sternbach, Abraham A.
2070 Grand Concourse
New York 57, N. Y.

Szafir, Paul
177 Nigh Street
Perth Amboy, N. J.

Telefeian, Alphonse
690 Congress Street
Portland, Maine

Terhune, William B.
Valley Road
New Canaan, Conn.

Thomson, Carroll S.
44 Madison Avenue
Morristown, N. J.

Tritt, Herman
365 West 263rd Street
New York 71, N. Y.

Turow, I. L.
390 East High Point Rd.
Peoria, Illinois

Victoroff, Victor M.
2231 Taylor Road
Cleveland 6, Ohio

Villamena, Diodato
806 Carroll Street
Brooklyn 31, N. Y.

Vlavianos, G.
Box A
Kings Park, N. Y.

Wallaert, Albert A. J.
916 Lakepointe (GP)
Detroit 30, Mich.

Wender, Louis
59 East 79th Street
New York 28, N. Y.

Wilcox, Paul H.
333 Sixth Street
Traverse City, Mich.

Yanof, Zale A.
2278 Ashland Avenue
Toledo 10, Ohio

Zaris, David
620 Thwaites Place
New York 60, N. Y.

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